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(54) Title: IMMUNE DIRECTION THERAPY		
(57) Abstract		
<p>Herein is described a specific amino acid sequence which exhibits specific Ion (bridge) pair arrays enclosed on at least one side by non polar hydrophobic transmembrane segments, as a mechanism used by many infectious agents and a number of cytokine inhibitory factors, such as Interleukin 10 and Prolactin Inhibitory factor and alfa-fetoprotein, to not only undermine the hosts immune defences but to also allow for the infection of target lymphoid tissue. It has been demonstrated that certain vaccines, when inoculated into a host, produced a range of neutralising antibodies but failed to prevent infection when that host is later challenged with live infectious organism. This present patent illustrates that when such vaccine inoculation is coupled with passive immunisation with mono or polyclonal antibodies to these specific amino acid sequences as specified herein that the host is then capable of overcoming the infectious challenge. Herein is described the therapeutic use of mono or polyclonal antibodies to these said specific sequences as a treatment for Acquired Immune Deficiency Syndrome (AIDS) and other disease states that persist due to the presence of a cytokine inhibitory factor of viral, fungal, bacterial or host origin such as Chronic Fatigue Syndrome where Interleukin 10 mimic molecules are responsible for a multitude of disease symptoms identified as indicative of Myalgic Encephalitis. Herein is described the therapeutic use of mono or polyclonal antibodies to these specific amino acid sequences as a combination therapy with vaccines and anti-viral agents to prevent side effects from certain immune modulation and anti-viral agents (e.g. DHEA and IL-12) which cause enhanced production of Interleukin 10 or AFP mimic molecules during therapy. Also herein is described the therapeutic use of these specific sequences either isolated from the organism source or produced by direct synthesis or recombinant protein synthesis. These peptides when administered to a patient suffering from an auto-immune disease, such as Multiple Sclerosis (MS), Lupus (systemic Lupus erythematoses) or diabetes or rheumatoid arthritis as limited examples or to transplant organ recipients, will allow the patient's immune state to be shifted to a Th₂ antibody dependent immune response and curtail the Th₁ (T cell dependent) immune attack which is evident in such immune malfunctions as MS and graft versus host disease. Certain dermatological conditions which are today treated by the use of corticosteroid creams and ointment may also be successfully treated by replacing the corticosteroid with these mimic immunosuppressive AFP/Interleukin 10 sequences outlined in this patent.</p>		

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IMMUNE DIRECTION THERAPY

It is identified in this patent that a very specific amino acid sequence which exhibits specific ion bridge pair arrays, especially if enclosed on at least one side by a non-polar hydrophobic transmembrane segment of at least one amino acid, can, if presented with a carrier to a cell membrane, induce endocytosis and cause activation of specific intracellular and extracellular events which would normally only result from the interaction of an Antigen MHC-II complex with both the T cell receptor (TCR) and the CD3 membrane complexes. These specific amino acid ion bridge pair sequences are only present within the cell membrane during proper functioning of the immune system and allow activating T cell clone expansion following antigen presentation. If this specific ion bridge pair enclosed on at least one side by hydrophobic segments is presented to the cell from a non immune source then increased cytoplasmic circulation from cell membrane of specific marker molecules occurs and this removes the normal immune functions of the cell types impacted by these specific peptide sequences. A proportion of amino acid sequences according to the present invention have demonstrated in a dose dependent manner the ability to down-regulate the expression of Ia molecules on human macrophages. Some in-vitro experiments suggest that direct T cell antigen interactions without the mediation of Ia bearing macrophages may result in the generation of antigen specific suppressor T cells. All experimental evidence indicates that the development of antigen-reactive clones of helper T cells requires the presence of Ia bearing cells in the tissue. This inhibition of expression on the membrane surface of these class II molecules (Ia) as produced with alfa-fetoprotein and/or cytokine inhibitory factor, signals the immune system to accept the appearance of new antigens as self to the immune system. Hence the often reported observation that an immune activation on polyclonal B cell activation producing

auto-antibodies follow certain viral, bacterial and parasitic infections (e.g. HIV, Malaria). The effects of these specific peptide ion-bridge pairs attached to a hydrophobic amino acid sequence demonstrate that they are the component peptide segments within both the alpha-fetoprotein and the cytokines molecules that are involved in the process of inducing tolerance and maintaining the tolerant state to infectious organisms presenting these sequences.

In identifying this specific type of sequence and its ability to generate specific immune signals together with its ability to enhance or trigger endocytosis of attached peptides or glycopeptides, we have been able to identify these specific amino acid sequences as a mechanism used by many infectious agents to not only undermine the hosts' immune defenses but to also allow for the penetration or infection of target lymphoid tissue.

Amino acids and residues thereof (i.e., amino acids in which one or more hydrogen atoms have been removed) are referred to herein by their 3-letter abbreviations, (e.g., "Lys" for Lysine) well known to those skilled in the art.

According to the present invention, there are therefore provided pharmaceutical compositions and methods of enhancing immune response in a patient suffering from immunodeficiency and/or one or more condition selected from the group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of bacterial, mycoplasmic, fungal parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;

(g) tuberculosis infection; and

(h) malarial infection,

comprising administering to the patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

C-X-A-B-Y-Z;

C-X-A-B-D;

C-X-A-B;

10 D-A-B-Y-Z; and

A-B-Y-Z;

wherein:

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

15 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

20 B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

The present invention also provides pharmaceutical compositions and methods of enhancing immune response, e.g., in a patient suffering from a condition as set forth above, comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

25

D-A-B-E;
D-A-B; and

A-B-E;

wherein:

5 D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

10 B is Glu or Asp;

and wherein said at least one compound comprises at least 4 amino acid residues. In specific aspects of the present invention, the compound can consist of 16 or fewer amino acid residues, or of 8 or fewer amino acid residues.

15 In specific aspects of the present invention, at least one compound can consist of 16 or fewer amino acid residues, 8 or fewer amino acid residues, or 4 or fewer amino acid residues.

In a preferred aspect of the present invention, the sub-sequence -A-B- further includes a hydrophobic amino acid residue "H", i.e., an amino acid residue selected from Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr on either end, 20 i.e., -H-A-B- or -A-B-H-.

The present invention further relates to the antibodies used in the methods of the invention.

In addition, any of the antibodies in accordance with the present 25 invention can be administered to a patient in addition to any known vaccine.

The present invention further relates to methods of reducing a patient's immune response, by administering any of the compounds described above which have a sub-sequence -A-B- or -B-A, preferably -H-A-B- or -H-B-A-. The present invention further relates to such compounds.

Suitable (3-amino acid) sequences which include a sub-sequence -H-A-B- or -H-B-A- for use in accordance with the present invention include the following:

- Ala-His-Asp; Ala-His-Glu; Ala-Lys-Asp; Ala-Lys-Glu; Ala-Arg-Asp;
 5 Ala-Arg-Glu; Ile-His-Asp; Ile-His-Glu; Ile-Lys-Asp; Ile-Lys-Glu; Ile-Arg-Asp;
 Ile-Arg-Glu; Leu-His-Asp; Leu-His-Glu; Leu-Lys-Asp; Leu-Lys-Glu; Leu-Arg-Asp;
 Leu-Arg-Glu; Met-His-Asp; Met-His-Glu; Met-Lys-Asp; Met-Lys-Glu;
 Met-Arg-Asp; Met-Arg-Glu; Phe-His-Asp; Phe-His-Glu; Phe-Lys-Asp;
 Phe-Lys-Glu; Phe-Arg-Asp; Phe-Arg-Glu; Pro-His-Asp; Pro-His-Glu;
 10 Pro-Lys-Asp; Pro-Lys-Glu; Pro-Arg-Asp; Pro-Arg-Glu; Trp-His-Asp;
 Trp-His-Glu; Trp-Lys-Asp; Trp-Lys-Glu; Trp-Arg-Asp; Trp-Arg-Glu;
 Val-His-Asp; Val-His-Glu; Val-Lys-Asp; Val-Lys-Glu; Val-Arg-Asp;
 Val-Arg-Glu; Ala-Asp-His; Ala-Glu-His; Ala-Asp-Lys; Ala-Glu-Lys;
 Ala-Asp-Arg; Ala-Glu-Arg; Ile-Asp-His; Ile-Glu-His; Ile-Asp-Lys; Ile-Glu-Lys;
 15 Ile-Asp-Arg; Ile-Glu-Arg; Leu-Asp-His; Leu-Glu-His; Leu-Asp-Lys;
 Leu-Glu-Lys; Leu-Asp-Arg; Leu-Glu-Arg; Met-Asp-His; Met-Glu-His;
 Met-Asp-Lys; Met-Glu-Lys; Met-Asp-Arg; Met-Glu-Arg; Phe-Asp-His;
 Phe-Glu-His; Phe-Asp-Lys; Phe-Glu-Lys; Phe-Asp-Arg; Phe-Glu-Arg;
 Pro-Asp-His; Pro-Glu-His; Pro-Asp-Lys; Pro-Glu-Lys; Pro-Asp-Arg;
 20 Pro-Glu-Arg; Trp-Asp-His; Trp-Glu-His; Trp-Asp-Lys; Trp-Glu-Lys;
 Trp-Asp-Arg; Trp-Glu-Arg; Val-Asp-His; Val-Glu-His; Val-Asp-Lys;
 Val-Glu-Lys; Val-Asp-Arg; and Val-Glu-Arg.

- Numerous suitable carrier compounds for use in accordance with the present invention would be readily apparent to those skilled in the art, and
 25 representative examples include Serum albumin precursor - rat; Acyl carrier protein - Escherichia coli; Serum Albumin precursor - human; S. typhimurium branched chain amino transport system II carrier; Branched - chain amino acid carrier; Ribosomal protein S16 - Escherichia coli; 3-Hydroxydecanoyl -{Acyl-Carrier-Protein} Dehydratase; Excitatory amino acid transporter 3 (sodium-

dependent; glutamate/aspartate transporter 3) (excitatory amino-acid carrier 1); Glutaredoxin 3; Cytochrome B5/C6; Transthyretin Precursor (prealbumin) (TBPA) (TTR); Phosphocarrier Protein HPR (Histidine-containing protein); Beta-Hexosaminidase alpha chain precursor; ACYL Carrier Protein (ACP);
5 Surfactin synthetase component; Sterol carrier protein 2 precursor; Insulin-Like growth factor binding protein 3 Precursor (IGFBP-3); Mitochondrial Brown Fat Uncoupling Protein (UCP); Thioredoxin; Oleoyl-hydrolase; Platelet factor 4; Lactose Permease; Keyhole Lipid hemocyanin (KLH); and Bovine Serum Albumin (BSA).

10 The antibodies of the present invention are humanised as per the following reference:

From cells to genes: how to make antibodies useful in human diagnosis and therapy. Zaccolo M, Malavasi F. Dipartimento di Genetica, Universita di Torino, Italy. Int J Clin Lab Res 1993; 23(4): 192-198.

15 The mono/polyclonal antibodies are made as per the following reference: Moller, G. (ed.): Engineered antibody molecules. Immunol. Rev. 1992, 130:1-212.

The present invention further relates to methods of vaccinating a patient against immunosuppressive sequences, by administering a compound
20 which corresponds with an immunosuppressive sequence, except that one or both of the members of at least one -A-B- sub-sequence is replaced with an analog, an antimetabolite or a D-amino acid corresponding to the replaced amino acid. The present invention also relates to such compounds. Examples of such immunosuppressive sequences include:

25 Asp-Arg-Ala-Ala-Asp-Gly-Gln-Pro-Ala-Gly (SEQ ID NO. 1);
HTLV-I gp21E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Trp-Glu-Gln-Gly-Gly-Leu-Cys-Lys-Ala-Leu-Gln-Glu-Gly-Cys-Arg-Phe (SEQ ID NO. 2);
HTLV-II gp21E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Trp-Glu-Gln-Gly-Gly-Leu-Cys-Lys-Ala-Ile-Gln-Glu-Gln-Cys-Cys-Phe (SEQ ID NO. 3);

MoLV p15E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Leu-
Lys-Glu-Gly-Gly-Leu-Cys-Ala-Ala-Leu-Lys-Glu-Glu-Cys-Cys-Phe (SEQ ID
NO. 4);

FeLV p15E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Ile-Leu-Phe-Leu-
5 Gln-Glu-Gly-Gly-Leu-Cys-Ala-Ala-Leu-Lys-Glu-Glu-Cys-Cys-Phe (SEQ ID
NO. 5); and

Vivax-1.

A variety of analogs which would be suitable for use according to the
present invention would be readily apparent to those skilled in the art.

10 Representative examples include analogs of Larginine including Lornithine,
L-Citrulline, L- α -Aminobutyrate, Agmatine (4-amino-1-guanidinobutane),
Putrescine (1,4-diaminobutane), glycocyamylglycine, glycocyamine,
taurocyamine, methylguanidine, L-Homoarginine, L-Argininosuccinic
anhydride (I), L-Argininic acid, L-Argininosuccinic anhydride (II), L-
15 Argininosuccinate (III), L-Argininosuccinate anhydride (IV), and LnitroArginine;
and analogs of Lysine including L-thialysine (S-(α -amino-ethyl)-L-cysteine),
D/L 4 oxalysine, β -Lysine, N⁵-Hydroxy-L-Arginine.

The present invention further relates to a method of treating a condition
selected from the group consisting of:

- 20 (a) immunodeficiency resultant from a viral infection;
(b) immunodeficiency resultant from one or more of the following,
bacterial, mycoplasmic, fungal and/or parasitic infections;
(c) immunodeficiency resultant from the growth of neoplastic tissue;
(d) immunodeficiency resultant from any cytokine or hormone
25 imbalance or imbalance of any natural product within the patient;
(e) myalgic encephalomyelitis (ME);
(f) post inoculation or viral infection fatigue syndrome;
(g) tuberculosis infection; and
(h) malarial infection,

in a patient in need of such treatment, comprising deleting genetic material from an infectious organism to prevent said genetic material from generating one or both amino acids in an amino acid sub-sequence "K" selected from the group consisting of Lys-Glu, Lys-Asp, Arg-Glu, Arg-Asp, His-Glu, His-Asp, Glu-Lys, Asp-Lys, Glu-Arg, Asp-Arg, Glu-His and Asp-His, and sub-sequences K which have at least one adjacent hydrophobic amino acid.

The present invention further relates to methods and pharmaceutical compositions described above, wherein the component A and the component B are separated by 1 or 2 amino acid residues.

In accordance with another preferred aspect of the present invention, there are provided sequences which consist of four distinct regions, i.e., R1-R2-R3-R4, in which:

R1 is a region of up to 5AA within which there is one to three AA from the group Lysine and/or Arginine

R2 is a short region of up to 2AA which does not contain any of the following Asp, Glu, Lys, Arg or His

R3 is a region of up to 7AA within which there may be one or two AA from the group Aspartic acid and/or Glutamic acid. The Aspartic acid or Glutamic closest to the R4 region is positioned within R3 to allow a minimum of two AA between these said acids and the R4 region.

R4 is a region of two AA containing one AA of either Lysine or Arginine attaching to region R3 and the other AA is either Aspartic acid or Glutamic acid.

Regions R1, R2 and R3 are considered the positioning regions of this specific AA sequence as they allow alignment of the AA sequence with cell membrane whereas R4 is considered the signalling sequence as this duo of peptides activates cell stimulation. This said peptide may be administered with a carrier moiety wherein the said carrier protein comprises bovine serum

albumin, human serum albumin, an immunoglobulin or a hormone. These peptides may be made to further possess sugar groups, normal serum components, lipids, phospholipids, etc. Naturally occurring organisms using peptides similar to those described herein for immune attack may be treated to deactivate their peptide immune activation mechanism by altering, by means known to those skilled in the art, one or more of either Lysine or Arginine existing in Region R1 and preferably in addition altering one or two of the AA in region R4 to remove the charge distribution of the said peptide. Vaccines may be manufactured using such techniques.

10 In accordance with another preferred aspect of the present invention, there are provided sequences which consist of four distinct regions, i.e., RA-RB-RC-RD, in which:

RA is a region of up to 5 AA within which there is one to three AA from the group Lysine and/or Arginine

15 RB is a short region of up to 2AA which does not contain any of: Asp, Glu, Lys, Arg or His.

RC is a region of up to 7AA within which there may be one or two AA from the group Aspartic acid and/or Glutamic acid. The Aspartic acid or Glutamic closest to the RD region is positioned within RC to allow a minimum of two AA between this said AA, if one exists, and the RD region. RD is a region of three or four AA containing one AA of either Lysine or Arginine attaching to region RC and one or two amino acids in the middle of the region containing AA from Polar and/or non-Polar with another AA at the end of the region which is either Aspartic acid or Glutamic acid.

25 Regions RA, RB and RC are considered the positioning regions of this specific AA sequence as they allow alignment of the AA sequence with cell membrane whereas RD is considered the signalling sequence as this duo of peptides activates cell stimulation. This said peptide may be administered with a carrier moiety wherein the said carrier protein comprises bovine serum

albumin, human serum albumin, an immunoglobulin or a hormone. These peptides may be made to further possess sugar groups, normal serum components, lipids, phospholipids etc. Naturally occurring organisms using peptides similar to those described herein for immune attack may be treated
5 to deactivate their peptide immune activation mechanism by altering, by means known to those skilled in the art, one or more of either Lysine or Arginine existing in Region RA and preferably in addition altering one or two of the charged AA in region RD to remove the charge distribution of the said peptide. Vaccines may be manufactured using such techniques.

10 The present invention also relates to treatments comprising administering to a patient any pharmaceutical formulations disclosed herein together with an antiviral therapy.

The large scale efforts to produce a broad spectrum vaccine candidate for Influenza Virus has proved impossible due to the rapid rate of mutation of
15 the outer coat of this virus. However, without the ability to attach and fuse and signal host immune cells in the body using those specific polar single ion bridge pair arrays of amino acid specific sequences, outlined herein, it is non-infectious. If these amino acid sequences are altered in the Influenza Virus, this virus then cannot undermine the hosts' immune system and
20 achieve cell entry or create immune dysfunction. This ability is restricted to a specific number of sequences, all of which must present to the cell membrane the charge distribution shown to activate endocytosis and TCR/CD3 cell activation and neutralise T cell immune surveillance as it relates to MHC-Class I and II. Therefore, if the infected host, human or
25 animal, already possesses neutralising antibodies to these amino acid changed dipole sequences as specified herein it will not be possible for infection to be established because these neutralising antibodies perform a dual function (A) they prevent anchorage and endocytosis of the infecting organism into the host cell thus preventing productive infection and (B) they prevent the

circulation in the plasma of these mimic Interleukin 10 or AFP type molecules which are released by infecting organisms. These specific said sequences confuse the normal signalling system involved in immune T and B cell activation since when applied to cells they trigger an intracellular Biochemical signal similar to when a T cell receptor (TCR) molecule coupled to a CD3 molecule interact with a MHC-II antigen complex, together with the fact that these sequences also cause increased turnover of surface receptor molecules such as the Interleukin I receptor molecule, thus leading to an increase of Interleukin I levels and cause a shift in T cell performance due to the shifting Th_1/Th_2 cytokine balance.

It has been demonstrated with non-protective vaccine candidate antigens which when previously inoculated into a host produced a range of neutralising antibodies but failed to prevent infection being established when that host was later challenged with live infectious organism. When the initial vaccine inoculation is coupled with passive immunisation with mono or polyclonal antibodies to these said specific sequences of the present invention that an immune response to the vaccine antigen from both T cell and B cell immune components results which includes antibodies to these hitherto unchallenged sequences results, the host is then capable of overcoming an infectious challenge without becoming infected or producing the usual antibody and autoantibody peak and subsequent immunosuppression normally associated with infections caused by organisms who utilise these specific amino acid sequences to direct the hosts immune signalling system towards a more pronounced B cell or Th_2 cytokine profiled response.

Malaria is one of the most important infectious diseases in the World; each year there are 270 million new infections resulting in over 100 million episodes of illness and approximately 2 million deaths. World-wide the malaria problem is getting worse each year. The reason for this worsening

situation include (A) increased levels of drug resistance on the part of the parasites, (B) increased levels of insecticide resistance on the part of the vectors. No vaccine has yet been produced which can successfully induce a protective antibody response. The reason for this is that although antibodies which cross react with many epitopes of the P. vivax circumsporozoite are produced in abundance by the current unprotective vaccine candidates, because of the immune blind spot or immunologically privileged sites offered by these specific sequences identified herein, like Interleukin 10 and AFP, these sequences are not visible to the host immune system which both allow the parasite to gain access to the host cell and to cause the non-specific polyclonal B cell activation and immunosuppressive (Interleukin 10 and/or AFP) like effects which are so universal for people suffering from parasites such as malaria, and Leishmania, the host cannot gain enough immune reactive monocytes to overcome the infection initially because these Interleukin 10/AFP mimic molecules carried by the infecting organism shuts down the vital Th₁ T cell response needed to clear intra-cellular infections. We have identified the specific polar array sequence on the coat protein of malaria which this organism uses like Influenza Virus to attach and activate endocytosis together with activating a Th₂ (B cell) response and subsequently undermining the host's immune response and allowing infection to take hold while still producing an array of neutralising antibodies which creates mutational pressure for the generation of more virulent strains of the organism within the host.

Our studies clearly demonstrated in mouse models that polyclonal or monoclonal antibodies generated to the above polar sequence arrays to these specific amino acid sequences either taken from specific sequences present in human alfa-fetoprotein or human Interleukin 10 resulted in protection of mice from challenge by malaria sporozoites. Therefore a vaccine for malaria which will enable a human to raise a protective antibody titre against malaria

sufficient to prevent infection may be manufactured by deleting from the antigenic peptide to be used in the vaccine these amino acid sequences displaying the specific polar arrays outlined in this patent. Another method expected to be more successful as a vaccine combination (because the immune system of primates including man appear to be blinded to these specific signal sequences) for protection is to use passive immunisation with either polyclonal or monoclonal antibodies to these said specific dipole immunosuppressive sequences generated either in animal human and/or tissue culture given either before or simultaneously with any of the current malaria vaccine candidates which previously could not produce a protective immune response. When these mono or polyclonal antibodies are given to the host in conjunction with the antigen the host's immune system does not produce the well documented polyclonal B cell activation of the host immune system and the immune system of the host so challenged will produce a protective antibody and T cell immune response which allows it to deal effectively with any later malaria infection challenge.

In malaria, as in other infections the said specific sequences, identified as a dipole amino acid sequence in this patent, when embedded in the cell membrane of the host activates the phosphatidylinositol pathway, which causes the release of Ca^{++} , the phosphorylation of cell proteins and the activation or enhanced activity of certain enzymes related to metabolism. This does not occur in the presence of antibodies to the disclosed specific sequences and the organism like malaria, Mycobacterium Tuberculosis, Leishmania, HIV and others are not able to cause metabolic and immune Th_2 activation and exhaustion. It is an important coincidence that in certain malaria endemic areas that genetic mutations that have caused the deletion of the metabolic activity control enzyme glucose-6-phosphate dehydrogenase has conferred on the host immunity to malaria. By intervening at an early stage of infection and neutralising certain properties of the malaria parasite

to alter cellular reactions by interfering with these specific membrane signal transduction sequences as defined herein it is possible to confer protective immunity to this organism.

The present invention utilises the novel discovery that certain amino acid sequences which exhibit specific ion (bridge) pair arrays enclosed on at least one side by non-polar hydrophobic transmembrane segments can be utilised to enhance the humoral antibody response and down-regulate the T cell or delayed-type hypersensitivity (DTH) response of humans and animals. These CD3/TCR mimic membrane interaction molecules which present as hydrophobic ion bridge pairs are utilised by both the organism itself as specific peptides and by cytokines and also by infectious agents to modulate immune response (A) during periods of reproductive foetal gestation as with the alpha-fetoprotein molecule to prevent foetal rejection by the maternal immune system and (B) during cytokine control of immune functions as with cytokine synthesis inhibitory factor (Th₂ cytokine) when a Th₂ cytokine profile is required or to curtail the uncontrolled Th₁ T4 cell immune response. These immunosuppressive cytokines are particularly evident following vaccination to enhance humoral immunity and secure antibody formation, and often causes the temporary disappearance of the Tuberculin reaction which is associated with Th₁ (DTH) response in patients following vaccination. (C) Infectious agents such as viruses (RNA & DNA) mycoplasma, bacteria, malaria and a wide array of human and animal parasites also carry these specific charged array of amino acid sequences which cause the down regulation of the Th₁ cytokine response and enhance the humoral (antibody mediated) immune response of their infected host.

Now that these specific control sequences have been identified and verified we herewith outline a number of therapeutic modalities that result from this new found ability to intervene therapeutically to control, neutralise or enhance specific immune type reactions dependent upon the nature of the

patient's or animal's own immune system status, infection or disease state.

Example

Anti-serum generated to these specific sequences as presented in AFP, Interleukin 10, EBV-BCRF1 and other peptides and as specified in amino acid sequence, listing enclosed, with this patent can be used to remove AFP mimic molecules from the circulation of immunosuppressed patients suffering from viral and/or bacterial and/or fungal, mycoplasmic or parasitic infections, which infection's principle method of defence against the host is to stimulate a Th2 cytokine response and curtail or abolish the Th1 cell mediated immune attack.

This invention relates to methods of treatment of persons and animals with indications of immunodeficiency, wherein the said indication is resultant from viral and/or retroviral infection and/or infectious parasites, bacteria and/or mycoplasma. The invention further relates to treatment with the above antiserum either poly or monoclonal in nature for establishing improved immuno response for persons and prophylactic treatment for persons where immuno-malfunction due to genetic pre-disposition or infection is considered a future risk.

The invention further relates to a screening method for vaccines, manufactured by the use of coat or other peptides from viral, bacterial, parasitic or mycoplasma, to determine and remove and/or neutralise inherent immune suppressive properties - such suppressive potential properties are determined by the manufactured vaccine's reactivity with the said specific amino acid sequences as outlined herein, be they synthetic or natural in origin, e.g. AFP, Th₂ cytokines, viral or bacterial coat peptides. In one embodiment, the host organism (man or animal) is treated with mono or polyclonal antibodies to any one or combination of the specific amino acid sequences as defined herein. This will result in the removal of Th₂ cytokine and AFP type mimic immunosuppressive peptides and initiate a Th₁ cell

response, allowing Interleukin 2 and gamma interferon synthesis to occur. Treatments used according to this invention employing the poly or monoclonal antiserum to these specific immune system inhibitory sequences are administered as treatments against viral, bacterial and mycoplasma and parasitic infections which cause immunosuppression by any suitable route including enteric, parenteral, topical, oral, rectal, nasal or vaginal routes. Parenteral routes include subcutaneous, intramuscular, intravenous and sublingual administration. The preferred route of administration would be an intravenous one.

10 The present invention further provides pharmaceutical formulations, for use in treatments against HIV/HTLV-I, II, III and other viral diseases and diseases caused by mycoplasma, bacteria or parasites.

 The present invention also relates to a method comprising inoculating into a patient a human, animal, synthetic or recombinant amino acid sequence with or without adjuvant, to produce an antibody response, the antibodies, mono or polyclonal will cause the binding of the immunosuppressive CD3/TCR mimic interaction molecules already present in the plasma of the infected host will be removed from the circulation of the infected host and normal immune function demonstrating a Th₁ cytokine profile, i.e. Interleukin 2 and gamma interferon, capable of resisting the infection will be re-established.

 Vaccines manufactured by the use of coat or other peptides from viral, bacterial, parasitic or mycoplasma may be screened to determine whether they possess these specific amino acid sequences which exhibit these specific ion bridge pair arrays capable of mimicking the actions of AFP or Th₂ cytokines and their inherent immune suppressive properties - such suppressive potential properties is determined by the manufactured vaccine's reactivity with any of the said specific amino acid sequences listed herein which may be removed or neutralised by the antiserum specified in this

patent.

The present invention also relates to a method of assaying body fluid from an animal, comprising contacting said body fluid with at least one antibody as described above.

- 5 The present invention further relates to a method of screening a vaccine, comprising contacting said vaccine with at least one antibody as described above.

Peptide Sequence Section

- 10 Firstly a series of documented and identified immunosuppressive sequences, encompassing both a known immunosuppressive peptide (CKS-17) and viral coat protein HTLV-III gp41 735-752 were selected and we by deletion or chemical modification of the referred amino acids Table 1 demonstrated that by compromising the charged amino acid dipole arrays within the hydrophobic segment of these peptides it was possible to neutralize
15 the immunosuppressive ability of these selected immunosuppressive sequences.

- Peptide synthesis and protein conjugation.* The peptides were assembled by solid-phase peptide synthesis on a Merrifield polystyrene resin as described previously (Kennedy, R.C., Henkel, R.D., Pauletti, D., Allan, J.S.,
20 Lee, T.H., Essex, M., and Dreesman, G.R., Science 231, 1556, 1986). (Chanh, T.C., Dreesman, G.R., Kanda, P., Linette, G.P., Sparrow, J.T., Ho, D.H., and Kennedy, R.C., EMBO J. 5, 3065, 1986). Protection of amino acid side chains during synthesis and cleavage of the peptide from the support by anhydrous hydrogen fluoride (HF) have been described previously (Kinnunen,
25 P.K.J., Jackson, R.L., Smith, L.C., Gottom, A.M., Jr., and Sparrow, J.T., Proc. Natl. Acad. Sci. USA 74, 4848, 1977). Peptides were purified by reverse-phase HPLC, and their compositions were verified by amino acid analysis and the presence of a single peak by HPLC. A tyrosine residue was added to either the amino or the carboxy terminus for monitoring peptide purification

and radiodination. A cysteine residue was added to either terminus for coupling via its free sulfhydryl to the carrier proteins keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA) using the MBS heterobifunctional crosslinker.

5 KLH- Keyhole Limpet Hemocyanin

BSA- Bovine Serum Albumin

Inhibition of mitogen-induced blastogenesis

To assess the inhibitory effects of the peptides AA sequences outlined in Table 1. Normal human blastogenic response to mitogens, PMN cells from
10 healthy donors were cultured in the absence or presence of various concentrations of peptides or peptides conjugated to carrier proteins followed by mitogen stimulation. The results of the experiments are shown in Table 2. Preincubation of normal PMN with the immunosuppressive peptides chosen before signal sequence neutralization either conjugated to either KLH or BSA
15 resulted in a preformed and dose - dependent suppression of PHA - induced proliferation. Upon amino acid signal sequence as specified in Table 1 chemical modification there was a significant reduction in the suppression of PHA induced proliferation.

The viability of peptide treated PMN as determined by trypan blue
20 exclusion staining was comparable to that of untreated PMN, showing that suppression of proliferation did not result from peptide-induced cytotoxicity.

Inhibition of the normal two - way mixed - lymphocyte reaction

The immunosuppressive peptides which clearly suppressed the proliferation of normal PMN in a two-way mixed lymphocyte reaction (MLR)
25 were not capable of demonstrating any form of suppression when the specific dipole signalling sequence as designated in Table 1 were chemically modified to neutralize the charge distribution on the dipole (Table 3).

In-vitro proliferation assays. Peripheral mononuclear cells (PMN) were obtained from normal HIV antibody-negative donors by density

gradient centrifugation through Hisopaque-1077 (Sigma Chemical Co., St. Louis, MO). The in-vitro proliferation assays were performed by incubating 10^5 cells/well in 96-well round-bottom microtiter plates in the absence or presence of various dilutions of peptides for 4 days in RPMI 1640 cultured medium (Grand Island Biological Co., Grand Island, NY) supplemented with 10% fetal calf serum (FCS). On the fourth day of culture, the cells were stimulated with phytohemagglutinin (PHA, Sigma) at a final dilution of 0.1%, or Con A (Sigma), or pokeweed mitogen (PWM, Sigma) at final concentrations of 10 μ g/ml. The cultures were allowed to incubate for an additional 2 days at which time 1 μ Ci of [3 H] thymidine (New England Nuclear Co., Boston, MA) was added to each well. After an additional 18hr in culture, the cells were harvested and processed for scintillation counting.

For PHA-induced proliferation of murine cells, normal 3- to 5-week-old BALB/C mice (Jackson Laboratories, Bar Harbor, ME) were sacrificed and their spleen cells were obtained through density gradient centrifugation. The spleen cells were used at a density of 5×10^4 /well and the assay was done as described above.

Two-way mixed-lymphocyte reaction. Peripheral mononuclear cells from MHC-mismatched donors were obtained as described above. Cells (5×10^4) from one individual were mixed with an equal number of cells from another individual in the absence or presence of peptides from Table 1 for 5 days. The cultures were pulsed with [3 H]-thymidine for the last 18 hr and harvested for scintillation counting.

Table 1

Immunosuppressive Peptides Used

- 1 HTLV - III B gp41 AA Sequence:
5 Tyr-Glu-Arg-Pro-Glu-Gly-Ile-Glu-Glu-Glu-Gly-Gly-Glu-Arg-Glu-Arg-
Glu-Arg-Ser-Gly-Cys (SEQ. ID NO. 34)
AA 735-752
- 2 CKS-17 AA Sequence:
Leu-Gln-Asn-Arg-Arg-Gly-Leu-Asp-Leu-Leu-Phe-Leu-Lys-Glu-Gly-
10 Gly-Leu (SEQ. ID NO. 35)
CKS-17 (A)

1(A) HTLV-III B gp41 modified

- These peptides have their arginyl residues modified by the use of
15 1,2 cycloheranedione as outlined in Mahley, R.W., J. of Biol. Chem. 1977
Vol. 252 pgs. 7279-7287

Table 2

**Suppression of Mitogen Induced Blastogenic Response
To Normal Human Mononuclear Cells**

5	Percentage Suppression of Blastogenic Response to		
	PHA	ConA	PWM
HTLV-III _B gp41 - KLH AA 735-752 5µg/ml	74	77	85
10 HTLV-III _B gp41 - KLH (modified) Modified as per Neutralization of charge Distribution on dipole	6	7	4
15 CKS-17 5µM Modified CKS-17 Modification caused by Chemical modification of	64	80	76
20 The charge on dipole sequence			

Table 3
Immunosuppressive Peptides Suppression
Of Mixed Lymphocyte Reaction

Thymidine Incorporation (cpm) with			
5	Medium	HTLV-III gp41	Modified HTLV-III gp41
		735-752 (5μg/ml)	735-752 5μg/ml (charged dipole neutralized)
	5224 ± 256	2800 ± 120 (45%)	5236 ± 211 (0%)
	5368 ± 106	2789 ± 163 (46%)	5334 ± 107 (0%)
10	Medium	CKS-17	CKS-17 (Modified) (charged dipole neutralized)
		4738 ± 96	947 ± 68 (80%)
	5372 ± 173	1074.4 ± 03 (83%)	4834 ± 80 (19%)

The only detectable changes in the physical and chemical properties of the modified HTLV-III gp41 and CKS-17 was increased electrophoretic mobility which reflected the neutralization of the positive charge on the granido group of arginine.

1(B) HTLV-III B gp41 Modification Reversed

This modified peptide is essentially restored to its original immunosuppressive capability when the modification to the arginyl residue is reversed by treatment with hydrosylamine.

The immunosuppressive peptides designed as per this patent may be neutralized in their ability to effect immune function if the amino acid charged dipole sequence is deleted or chemically modified so that the charged chemical groups on the dipole amino acids, be they positive or negative, are either both or individually left without an electrostatic charge component. This has been demonstrated for this patent Tables 2/3 to effectively remove any immunosuppressive characteristics and could very easily accomplish the same end for intact viruses or bacteria should their genetic codes be deleted for these specific amino acids or their outer coats neutralized to these signal dipole sequences.

Those of skill in the art would readily be able to determine where an ion bridge pair exists in a particular sequence, e.g., an immunosuppressive sequence, and determine which ion bridge pairs are responsible for the immunosuppressive activity, by routine experimentation in view of the information contained herein.

The present invention further relates to pharmaceutical compositions and methods of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to the patient an immunosuppressive or immunoregulatory effective amount of a pharmaceutical formulation comprising at least two Th₂ cytokines, for example, wherein the at least two Th₂ cytokines include Interleukin 10 and Interleukin 4.

In relation to the administration of anti-serum to Interleukin-10 and also the combination therapy of Interleukin-10 and Interleukin-4 the dose ranging were as follows:

Interleukin-10 alone - 2 mg per day over a period of 10 days by IV.
Combination therapy - two trials.

Trial 1 : 2 mg per day of anti-serum to IL-10 on each alternative day and 2 mg per day of anti-serum to IL-4 on each other alternative day.

Administration by IV.

Trial 2 : infusion of 4 mg of a combination (50/50) of IL-10/IL-4 on days 1,3,5,9,11 and 14. - This dose range would vary and the ratio of cytokines

administered depending on the disease condition.

These agents as per this patent are administered in an amount, which provides circulating levels of about 1-150 µg/ml of each agent.

5 The present invention further relates to pharmaceutical compositions and methods of treatment of graft vs. host disease in a patient in need of such treatment, comprising administering to the patient Interleukin 10 and Interleukin 4.

10 The present invention further relates to pharmaceutical compositions and methods of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to the patient Interleukin 10, Interleukin 4 and at least one of antagonist of Interleukin 10 and antagonist of Interleukin 4.

15 The present invention further relates to pharmaceutical compositions and methods of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient Interleukin 10 and Interleukin 4 and at least one of agonist of Interleukin 10 and agonist of Interleukin 4.

20 The present invention further relates to pharmaceutical compositions and methods of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient anti-serum to Interleukin 10 and anti-serum to Interleukin 4

25 The present invention further relates to pharmaceutical compositions and methods of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient anti-serum to Interleukin 10 and at least one of antagonist of Interleukin 4 and agonist of Interleukin 4.

30 The present invention further relates to pharmaceutical compositions and methods of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient anti-serum to Interleukin 4 and at least one of antagonist of Interleukin 10 and agonist of Interleukin 10.

When rabbit antibodies to human Interleukin 10 was administered to

AIDS patients for a one week period by an IV route their cytotoxic CD8 cells and natural killer cell numbers increased within 24 hours and this resulted in a simultaneous increase in viral load levels as measured by PCR (RNA). However, quantitative culture techniques showed a decline to zero levels. The reason for the above would appear to be that the enhanced CD8 cytotoxic and natural killer cell attack on HIV infected cells increased the amount of HIV viral RNA and viral peptide present in the blood as a result of the killing of infected cells. The fact that quantitative culture decreased to zero means that the viral particles present were not viable or infectious viruses. However, no improvement in percentage or absolute number of CD4 (T4) cells was recorded and the Th₁ immune function did not show improvement. After 3 months from the termination of the above therapy with antibodies to Interleukin 10, HIV viral load returned to its pre-treatment level and his CD4 (T4) cell count decreased by 50%. This demonstrated that the anti-serum to Interleukin 10 had been capable of activating CD8 cytotoxic and natural killer cells and causing a dramatic reduction in viral load. However, the CD4 (T4) immune system cells had not improved so that when following therapy his CD8 and natural killer cells lost their function, dormant virus was awakened by the Interleukin 10 antibody therapy and new viral replication could not be kept in check without a complement of active CD4 cells.

This same patient was then administered a combination therapy which involved rabbit IgG antibodies generated to both human Interleukin 10 and human Interleukin 4. It had been determined from in-vitro studies with the patients blood that native Interleukin 4 levels were elevated and this was preventing the recovery of the CD4 (T4) cell component of his immune system.

The patient was administered the two antibodies to Interleukin 10 and Interleukin 4 for 2 weeks. Following this the patient's HIV viral load again increased when monitored by PCR RNA and decreased to zero after 4 weeks. However, on this occasion his CD4 (T4) cell count both in absolute number and percentage increase from 9% to 15% within 4 days of

therapy commencing. After the 3 month period out from the termination of the combination therapy, CD4 (T4) cell count continued to remain elevated and HIV viral load was still non-detectable.

Suitable dosages in accordance with the present invention depend
5 on many factors, e.g. the patient's weight, the mode of administration, the frequency of administration, the type of affliction being treated or prevented, whether the infection presently exists, and if so, to what degree. Suitable dosages for given situations can readily be determined by those skilled in the art without undue experimentation.

10 The total treatment time according to the present invention will vary from patient to patient based on sound medical judgement and factors particular to the patient being treated, such as, for example, the age and physical condition of the patient. Those skilled in the art can easily determine suitable total treatment time on a patient-by-patient basis.

15 The following is a description of a suitable protocol in accordance with the present invention. However, the present invention is not limited by the following Example, and variations will be apparent to those skilled in the art without departing from the spirit of the present invention.

20 **PROTOCOL FOR ADMINISTRATION OF AN IMMUNOGLOBULIN IgG
ANTIBODY AGAINST A COMBINATION OF TH2 CYTOKINES.**

1.0 INTRODUCTION

The Human Immunodeficiency Virus Type 1 (HIV-1) is the etiological agent of Acquired Immune Deficiency Syndrome(AIDS) (Barre-Sinoussi, F., Chermann, J.C., et al, Isolation of a T-lymphotrophic Retrovirus From a
25 Patient at Risk for Acquired Immunodeficiency Syndrome (AIDS), Science (1984) 224, 500-503; Gallo, R.C., Salahuddin, S.Z., et al, Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) From Patients with AIDS and at Risk for AIDS. Science (1984) 224, 500-503). AIDS is characterised as a profound breakdown in host's cellular and humoral
30 immunity and increased susceptibility to a wide range of opportunistic infections. One of the consequences of this immune dysfunction is a marked depletion in absolute CD4+ cells in HIV-infected individuals.

Studies over the past years have demonstrated that the destruction of the immune system by HIV-1 is a chronic process, starting at the moment of infection. The results indicate that strategies for effective therapeutic intervention using antibodies to these specific mimic CD3/TCR peptide interaction dipole sequences should start early in infection to prevent irreversible damage occurring to the immune system, since it has been demonstrated in HIV that an early loss of CD3/TCR mediated T cell activation is evident. This imbalance in turn effects monocyte and B cell function.

Recent studies have established the functional binding and immunosuppressive similarities between specific amino acid charged sequences present on the alfa-fetoprotein molecule and on and Th₂ cytokine peptides and certain HIV envelope amino acid sequences. Laboratory data demonstrates that immunoglobulin G (IgG) or IgM to the said specific amino acid sequence inhibits syncytial formation and prevents HIV-1 laboratory strains MN, RF, and IIIB replication in C8166-45 cells (lymphocyte cell-line) in-vitro. In addition, IgG to the said amino acid sequence inhibits replication of HIV-1_{BAL} in fresh macrophage culture in a dose-dependent manner.

1.2 RATIONALE

The basic rationale for using this therapy is the understanding that there exists a functional binding and immunosuppression similarity between certain peptides containing specific ion pair arrangements of amino acids enclosed within two hydrophobic amino acids present within the AFP molecule Interleukin 10 and specific external HIV glycoproteins together with other specific viral coat peptides and glycopeptides. This discovery shows that as the body defends itself against the HIV virus by producing antibodies to specific viral coat proteins, these antibodies, while restricting in a normal antibody fashion the HIV virus, are themselves together with certain viral glycopeptides sequences identified herein and produced by the infecting virus are inherently immunosuppressive in that they perform a similar task as AFP or Th₂ cytokine peptides in that they

selectively down regulate the T cell dependent immune system in favour of a humoral, B cell response which although it produces neutralising antibodies to the infectious agent (e.g. malaria, HIV, Tuberculoses, Leishmania) also allows the infective agent to persist and reproduce within the host cells and to ultimately undermine its immune status.

The major histocompatibility complex (MHC) is a collection of 40-50 genes arrayed within a long continuous stretch of DNA on chromosome 6 in humans. The MHC is referred to as the HLA complex in humans. The MHC genes are organised into regions encoding three classes of molecules: Class I, Class II and Class III. The Class I genes encode glycoproteins expressed on the surface of nearly all nucleated cells, where they present peptide antigens of altered self-cells necessary for the activation of T_C cells. The Class II genes encode glycoproteins expressed primarily on antigen-presenting cells (macrophages, dendritic cells, and B cells), where they present processed antigenic peptides to T cells. The Class III genes encode somewhat different products that are also associated with the immune process. These include a number of soluble serum proteins (including components of the complement system), steroid 21-hydroxylase enzymes, and tumour necrosis factors.

The administration of antibodies poly or mono clonal to these specific CD3/TCR mimic molecules will cause an immediate antibody-dependent cell-mediated cytotoxicity (ADCC) stimulated reduction in Viral Load as measured by the culturing of peripheral blood mononuclear cells and following the removal of the mimic Th₂ cytokine/AFP like viral peptide molecules and in the patient's blood we should see a re-awakening of a CD8 cytotoxic T cell reaction directed against HIV infected cells and this will coincide with a second HIV Viral Load reduction. Also in patients who have received this antibody therapy we should see the generation of Interleukin 2 and gamma interferon and a dramatic increase in T4 cell number, together with a decrease in PCR and Quantitative Viral culture levels.

A number of white blood cells have cytotoxic potential and express

membrane receptors for the Fc region of the antibody IgG molecule. When this antibody is specifically bound to a target cell which occurs when these specific poly or monoclonal antibodies to these sequences present on AFP, and Th₂ cytokines bind to HIV infected cells or free viral peptides causing immune Th2 shift. These cytotoxic Fc receptor-bearing cells can bind to the antibodies' Fc region, and thus to the infected HIV cells, and subsequently cause lysis of these cells. Although the cytotoxic cells involved are non-specific, the specificity of the antibody to a common immunosuppressive mimic peptide present on Th₂ cytokines peptides/AFP present on a large number of infecting organisms directs them to HIV infected target cells. This type of cytotoxicity is referred to as antibody-dependent cell-mediated cytotoxicity (ADCC). The variety of cells that have been shown to exhibit ADCC include NK cells, macrophages, monocytes, neutrophils, and eosinophils.

2.0 OBJECTIVES

2.1 To provide for an administration of monoclonal antibodies to these specified sequences present on AFP and Th₂ cytokines and infectious organisms to HIV+ patients.

2.2 To monitor immune system functioning before and after the administration of these mono or polyclonal antibodies.

2.3 To monitor the effect of these type of antibody on cutaneous lesions in those study participants who have Kaposi's Sarcoma.

2.4 To monitor viral load in patient's peripheral blood mononuclear cells prior to beginning, during and post this type of antibody infusion therapy.

2.5 To monitor the course or incidence of opportunistic infections in the study participants.

2.6 To determine the safety of these type of antibody administration in persons with HIV disease.

3.0 CLINICAL ENDPOINTS

To confirm that these antibodies either poly or monoclonal are of therapeutic benefit for widespread use in HIV disease based on the following criteria.-

- 3.1 Changes in T-cell phenotyping and cytokine profile.
- 3.2 Changes in the size, colour intensity, and palpable skin characteristics of cutaneous Kaposi's sarcoma lesions.
- 3.3 Changes in HIV load burden as indicated by endpoint - dilution
- 5 culture quantitation in peripheral - blood mononuclear cells.
- 3.4 Changes in p24 antigen level.
- 3.5 Changes in Beta-2-microglobulin level
- 3.6. Appearance of new or improvement of active opportunistic infections.
- 10 3.7 Changes in system functioning (liver, kidney, haematology).

Claims:

1. A method of enhancing immune response in a patient suffering from a condition selected from the group consisting of:
- (a) immunodeficiency resultant from a viral infection;
 - 5 (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
 - (c) immunodeficiency resultant from the growth of neoplastic tissue;
 - (d) immunodeficiency resultant from any cytokine or hormone
 - 10 imbalance or imbalance of any natural product within the patient;
 - (e) myalgic encephalomyelitis (ME);
 - (f) post inoculation or viral infection fatigue syndrome;
 - (g) tuberculosis infection; and
 - (h) malarial infection,
 - 15 comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:
- C-X-A-B-Y-Z;
 - 20 C-X-A-B-D;
 - C-X-A-B;
 - D-A-B-Y-Z; and
 - A-B-Y-Z;
- wherein:
- 25 X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;
 - Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;
 - D is an amino acid sub-sequence comprising at least one amino
 - 30 acid residue;

A is Lys, Arg or His;
B is Glu or Asp;
C is a carrier compound residue;
Z is a carrier compound residue.

- 5 2. A method as recited in claim 1, wherein said at least one compound consists of 16 or fewer amino acid residues.
3. A method as recited in claim 1, wherein said at least one compound consists of 8 or fewer amino acid residues.
4. A method as recited in claim 1, wherein said at least one
10 compound consists of 4 or fewer amino acid residues.
5. A method of enhancing immune response in a patient suffering from a condition selected from the group consisting of:
- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following,
15 bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- 20 (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,
- comprising administering to said patient an immune response enhancing
25 effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:
- D-A-B-E;

D-A-B; and

A-B-E;

wherein:

D is an amino acid sub-sequence comprising at least one amino
5 acid residue;

E is an amino acid sub-sequence comprising at least one amino acid
residue;

A is Lys, Arg or His;

B is Glu or Asp;

10 and wherein said at least one compound comprises at least 4 amino
acid residues.

6. A method as recited in claim 5, wherein said at least one
compound consists of 16 or fewer amino acid residues.

7. A method as recited in claim 5, wherein said at least one
15 compound consists of 8 or fewer amino acid residues.

8. A method of treating a condition selected from the group
consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following,
20 bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic
tissue;
- (d) immunodeficiency resultant from any cytokine or hormone
imbalance or imbalance of any natural product within the patient;
- 25 (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,

in a patient in need of such treatment, comprising administering to said

patient an

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- 5 (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- 10 (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; or
- (h) malarial infection,

treatment effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment
15 thereof, generated to at least one compound selected from the group consisting of:

- C-X-A-B-Y-Z;
- C-X-A-B-D;
- C-X-A-B;
- 20 D-A-B-Y-Z; and
- A-B-Y-Z;

wherein:

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

25 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

30 B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

9. A method as recited in claim 8, wherein said at least one compound consists of 16 or fewer amino acid residues.

10. A method as recited in claim 8, wherein said at least one compound consists of 8 or fewer amino acid residues.

5 11. A method as recited in claim 8, wherein said at least one compound consists of 4 or fewer amino acid residues.

12. A method of treating a condition selected from the group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- 10 (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone
- 15 imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,

20 in a patient in need of such treatment, comprising administering to said patient an

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- 25 (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic Encephalomyelitis (ME);

- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; or
- (h) malarial infection,

treatment effective amount of a pharmaceutical formulation comprising at
5 least one polyclonal or monoclonal antibody, or at least one Fab fragment
thereof, generated to at least one compound selected from the group
consisting of:

D-A-B-E;

D-A-B; and

10 A-B-E;

wherein:

D is an amino acid sub-sequence comprising at least one amino
acid residue;

E is an amino acid sub-sequence comprising at least one amino acid
15 residue;

A is Lys, Arg or His;

B is Glu or Asp;

and wherein said at least one compound comprises at least 4 amino
acid residues.

20 13. A method as recited in claim 12, wherein said at least one
compound consists of 16 or fewer amino acid residues.

14. A method as recited in claim 12, wherein said at least one
compound consists of 8 or fewer amino acid residues.

25 15. A method of enhancing immune response in a patient suffering
from immunodeficiency, comprising administering to said patient an
immune response enhancing effective amount of a pharmaceutical
formulation comprising at least one polyclonal or monoclonal antibody, or
at least one Fab fragment thereof, generated to at least one compound
selected from the group consisting of:

C-X-A-B-Y-Z;
C-X-A-B-D;
C-X-A-B;
D-A-B-Y-Z; and

5 A-B-Y-Z;
wherein:

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

10 D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

15 C is a carrier compound residue;

Z is a carrier compound residue.

16. A method of vaccinating against an immunodeficiency producing infection or condition selected from the group consisting of:

- (a) viral infections;
- 20 (b) one or more of bacterial, mycoplasmic, fungal and parasitic infections;
- (c) growth of neoplastic tissue;
- (d) any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- 25 (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,

in a patient in need of such vaccination, comprising administering to said patient a vaccination effective amount of a pharmaceutical formulation comprising:

at least one vaccine against said condition; and
at least one polyclonal or monoclonal antibody, or at least one Fab
fragment thereof, generated to at least one compound selected from the
group consisting of:

5 C-X-A-B-Y-Z;
C-X-A-B-D;
C-X-A-B;
D-A-B-Y-Z; and
A-B-Y-Z;

10 wherein:

X is a covalent bond or an amino acid sub-sequence comprising at
least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at
least one amino acid residue;

15 D is an amino acid sub-sequence comprising at least one amino
acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

C is a carrier compound residue;

20 Z is a carrier compound residue.

17. A method as recited in claim 16, wherein said at least one
compound consists of 16 or fewer amino acid residues.

18. A method as recited in claim 16, wherein said at least one
compound consists of 8 or fewer amino acid residues.

25 19. A method as recited in claim 16, wherein said at least one
compound consists of 4 or fewer amino acid residues.

20. A method of vaccinating against a condition selected from the
group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic
5 tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- 10 (g) tuberculosis infection; and
- (h) malarial infection,

in a patient in need of such vaccination, comprising administering to said patient a vaccination effective amount of a pharmaceutical formulation comprising:

- 15 at least one vaccine against said condition; and
- at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

- D-A-B-E;
- 20 D-A-B; and
- A-B-E;

wherein:

- D is an amino acid sub-sequence comprising at least one amino
acid residue;
- 25 E is an amino acid sub-sequence comprising at least one amino acid
residue;

A is Lys, Arg or His;

B is Glu or Asp;

- and wherein said at least one compound comprises at least 4 amino
30 acid residues.

21. A method as recited in claim 20, wherein said at least one

compound consists of 16 or fewer amino acid residues.

22. A method as recited in claim 20, wherein said at least one compound consists of 8 or fewer amino acid residues.

23. A method of enhancing immune response in a patient suffering
5 from a condition selected from the group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic
10 tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- 15 (g) tuberculosis infection; and
- (h) malarial infection,

comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof,
20 generated to at least one compound selected from the group consisting of:

- C-X-H-A-B-Y-Z;
- C-X-H-A-B-D;
- C-X-H-A-B;
- D-H-A-B-Y-Z;
- 25 H-A-B-Y-Z;
- C-X-A-B-H-Y-Z;
- C-X-A-B-H-D;
- C-X-A-B-H;
- D-A-B-H-Y-Z; and
- 30 A-B-H-Y-Z;

wherein:

H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

10 A is Lys, Arg or His;

B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

24. A method as recited in claim 23, wherein said at least one compound consists of 16 or fewer amino acid residues.

25. A method as recited in claim 23, wherein said at least one compound consists of 8 or fewer amino acid residues.

26. A method as recited in claim 23, wherein said at least one compound consists of 4 or fewer amino acid residues.

20 27. A method of enhancing immune response in a patient suffering from a condition selected from the group consisting of:

(a) immunodeficiency resultant from a viral infection;

(b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;

25 (c) immunodeficiency resultant from the growth of neoplastic tissue;

(d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;

- (e) myalgic encephalomyelitis (ME);
(f) post inoculation or viral infection fatigue syndrome;
(g) tuberculosis infection; and
(h) malarial infection,
- 5 comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:
- 10 D-H-A-B-E;
D-H-A-B;
H-A-B-E;
D-A-B-H-E;
D-A-B-H; and
A-B-H-E;
- 15 wherein:
- H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;
- D is an amino acid sub-sequence comprising at least one amino acid residue;
- 20 E is an amino acid sub-sequence comprising at least one amino acid residue;
- A is Lys, Arg or His;
B is Glu or Asp;
- and wherein said at least one compound comprises at least 4 amino
- 25 acid residues.

28. A method as recited in claim 27, wherein said at least one compound consists of 16 or fewer amino acid residues.

29. A method as recited in claim 27, wherein said at least one compound consists of 8 or fewer amino acid residues.

30. A method of treating a condition selected from the group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following,
5 bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- 10 (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,

in a patient in need of such treatment, comprising administering to said
15 patient an

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following,
bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic
20 tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- 25 (g) tuberculosis infection; or
- (h) malarial infection,

treatment effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group
30 consisting of:

C-X-H-A-B-Y-Z;

C-X-H-A-B-D;

C-X-H-A-B;

D-H-A-B-Y-Z;

H-A-B-Y-Z;

C-X-A-B-H-Y-Z;

5 C-X-A-B-H-D;

C-X-A-B-H;

D-A-B-H-Y-Z; and

A-B-H-Y-Z;

wherein:

10 H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

15 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

20 C is a carrier compound residue;

Z is a carrier compound residue.

31. A method as recited in claim 30, wherein said at least one compound consists of 16 or fewer amino acid residues.

32. A method as recited in claim 30, wherein said at least one
25 compound consists of 8 or fewer amino acid residues.

33. A method as recited in claim 30, wherein said at least one compound consists of 4 or fewer amino acid residues.

34. A method of treating a condition selected from the group

consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- 5 (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- 10 (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,

in a patient in need of such treatment, comprising administering to said patient an

- 15 (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- 20 (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic Encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; or
- 25 (h) malarial infection,

treatment effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

- 30 D-H-A-B-E;
- D-H-A-B;
- H-A-B-E;

D-A-B-H-E;
D-A-B-H; and
A-B-H-E;

wherein:

5 H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid
10 residue;

A is Lys, Arg or His;

B is Glu or Asp.

35. A method as recited in claim 34, wherein said at least one compound consists of 16 or fewer amino acid residues.

15 36. A method as recited in claim 34, wherein said at least one compound consists of 8 or fewer amino acid residues.

37. A method of enhancing immune response in a patient suffering from immunodeficiency, comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical
20 formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

C-X-H-A-B-Y-Z;

C-X-H-A-B-D;

25 C-X-H-A-B;

D-H-A-B-Y-Z;

H-A-B-Y-Z;

C-X-A-B-H-Y-Z;

C-X-A-B-H-D;

C-X-A-B-H;
D-A-B-H-Y-Z; and
A-B-H-Y-Z;

wherein:

5 H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

10 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

15 C is a carrier compound residue;

Z is a carrier compound residue.

38. A method of enhancing immune response in a patient suffering from immunodeficiency, comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical
20 formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

R1-R2-R3-R4

wherein:

25 R1 is a region of up to 5AA within which there is one to three AA from the group Lysine and/or Arginine;

R2 is a short region of up to 2AA which does not contain any of the following Asp, Glu, Lys, Arg or His;

30 R3 is a region of up to 7AA within which there may be one or two AA from the group Aspartic acid and/or Glutamic acid. The Aspartic acid or Glutamic closest to the R4 region is positioned within R3 to allow a

minimum of two AA between these said acids and the R4 region; and

R4 is a region of two AA containing one AA of either Lysine or Arginine attaching to region R3 and the other AA is either Aspartic acid or Glutamic acid.

- 5 39. A method of enhancing immune response in a patient suffering from immunodeficiency, comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound
10 selected from the group consisting of:

RA-RB-RC-RD, wherein:

RA is a region of up to 5 AA within which there is one to three AA from the group Lysine and/or Arginine;

15 RB is a short region of up to 2AA which does not contain any of Asp, Glu, Lys, Arg or His;

RC is a region of up to 7AA within which there may be one or two AA from the group Aspartic acid and/or Glutamic acid wherein the Asp or Glu closest to the RD region is positioned within RC to allow a minimum of two AA between this said AA, if one exists, and the RD region; and

20 RD is a region of three or four AA containing one AA of either Lysine or Arginine attaching to region RC and one or two amino acids in the middle of the region containing AA from Polar and/or non-Polar with another AA at the end of the region which is either Asp or Glu.

- 25 40. A method of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient an immunosuppressive or immunoregulatory amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group
30 consisting of:

C-X-A-B-Y-Z;
C-X-A-B-D;
C-X-A-B;
D-A-B-Y-Z; and
5 A-B-Y-Z;

wherein:

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

10 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

15 C is a carrier compound residue;

Z is a carrier compound residue.

41. A method of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient an immunosuppressive or immunoregulatory effective amount of a
20 pharmaceutical formulation comprising at least two Th₂ cytokines.

42. A method as recited in claim 41, wherein said at least two Th₂ cytokines include Interleukin 10 and Interleukin 4.

43. A method of treatment of graft vs. host disease in a patient in need of such treatment, comprising administering to said patient Interleukin
25 10 and Interleukin 4.

44. A method of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient Interleukin 10, Interleukin 4 and at least one of antagonist of

Interleukin 10 and antagonist of Interleukin 4.

45. A method of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient Interleukin 10 and Interleukin 4 and at least one of agonist of Interleukin 10 and agonist of Interleukin 4.

46. A method of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient anti-serum to Interleukin 10 and anti-serum to Interleukin 4

47. A method of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient anti-serum to Interleukin 10 and at least one of antagonist of Interleukin 4 and agonist of Interleukin 4.

48. A method of providing an immunosuppressive or immunoregulatory effect in a patient, comprising administering to said patient anti-serum to Interleukin 4 and at least one of antagonist of Interleukin 10 and agonist of Interleukin 10.

49. A method of enhancing immune response in a patient suffering from a condition selected from the group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;

(g) tuberculosis infection; and

(h) malarial infection,

comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one

5 polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

C-X-A-Q-B-Y-Z;

C-X-A-Q-B-D;

C-X-A-Q-B;

10 D-A-Q-B-Y-Z; and

A-Q-B-Y-Z;

wherein:

Q is a sub-sequence consisting of one or two amino acid residues;

X is a covalent bond or an amino acid sub-sequence comprising at
15 least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

20 A is Lys, Arg or His;

B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

50. A method of enhancing immune response in a patient suffering
25 from a condition selected from the group consisting of:

(a) immunodeficiency resultant from a viral infection;

(b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;

(c) immunodeficiency resultant from the growth of neoplastic
30 tissue;

(d) immunodeficiency resultant from any cytokine or hormone

imbalance or imbalance of any natural product within the patient;

- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- 5 (h) malarial infection,

comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

- 10 D-A-Q-B-E;
- D-A-Q-B; and
- A-Q-B-E;

wherein:

Q is a sub-sequence consisting of one or two amino acid residues;

- 15 D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

- 20 B is Glu or Asp;

and wherein said at least one compound comprises at least 4 amino acid residues.

51. A method of vaccinating against an immunodeficiency producing infection or condition selected from the group consisting of:

- 25 (a) viral infections;
- (b) one or more of bacterial, mycoplasmic, fungal and parasitic infections;
- (c) growth of neoplastic tissue;
- (d) any cytokine or hormone imbalance or imbalance of any
- 30 natural product within the patient;
- (e) myalgic encephalomyelitis (ME);

- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,

in a patient in need of such vaccination, comprising administering to said
5 patient a vaccination effective amount of a pharmaceutical formulation
comprising:

at least one vaccine against said condition; and

at least one polyclonal or monoclonal antibody, or at least one Fab
fragment thereof, generated to at least one compound selected from the

10 group consisting of:

C-X-A-Q-B-Y-Z;

C-X-A-Q-B-D;

C-X-A-Q-B;

D-A-Q-B-Y-Z; and

15 A-Q-B-Y-Z;

wherein:

Q is a sub-sequence consisting of one or two amino acid residues;

X is a covalent bond or an amino acid sub-sequence comprising at
least one amino acid residue;

20 Y is a covalent bond or an amino acid sub-sequence comprising at
least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino
acid residue;

A is Lys, Arg or His;

25 B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

52. A method of vaccinating against a condition selected from the
group consisting of:

- 30 (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following,

- bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone
- 5 imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,
- 10 in a patient in need of such vaccination, comprising administering to said patient a vaccination effective amount of a pharmaceutical formulation comprising:
- at least one vaccine against said condition; and
- at least one polyclonal or monoclonal antibody, or at least one Fab
- 15 fragment thereof, generated to at least one compound selected from the group consisting of:
- D-A-Q-B-E;
- D-A-Q-B; and
- A-Q-B-E;
- 20 wherein:
- Q is a sub-sequence consisting of one or two amino acid residues;
- D is an amino acid sub-sequence comprising at least one amino acid residue;
- E is an amino acid sub-sequence comprising at least one amino acid
- 25 residue;
- A is Lys, Arg or His;
- B is Glu or Asp;
- and wherein said at least one compound comprises at least 4 amino acid residues.
- 30 53. A method of enhancing immune response in a patient suffering from a condition selected from the group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic
- 5 tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- 10 (g) tuberculosis infection; and
- (h) malarial infection,

comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof,

15 generated to at least one compound selected from the group consisting of:

- C-X-H-A-Q-B-Y-Z;
- C-X-H-A-Q-B-D;
- C-X-H-A-Q-B;
- D-H-A-Q-B-Y-Z;
- 20 H-A-Q-B-Y-Z;
- C-X-A-Q-B-H-Y-Z;
- C-X-A-Q-B-H-D;
- C-X-A-Q-B-H;
- D-A-Q-B-H-Y-Z; and
- 25 A-Q-B-H-Y-Z;

wherein:

Q is a sub-sequence consisting of one or two amino acid residues;

H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

30 X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at

least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

5 B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

54. A method of enhancing immune response in a patient suffering from a condition selected from the group consisting of:

- 10 (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- 15 (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- 20 (h) malarial infection,

comprising administering to said patient an immune response enhancing effective amount of a pharmaceutical formulation comprising at least one polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

25 D-H-A-Q-B-E;

D-H-A-Q-B;

H-A-Q-B-E;

D-A-Q-B-H-E;

D-A-Q-B-H; and

30 A-Q-B-H-E;

wherein:

Q is a sub-sequence consisting of one or two amino acid residues;

H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

and wherein said at least one compound comprises at least 4 amino acid residues.

55. A method of reducing immune response in a patient in need of such treatment, comprising administering to said patient an immune response reducing effective amount of a pharmaceutical formulation comprising at least one compound selected from the group consisting of:

C-X-A-B-Y-Z;

C-X-A-B-D;

C-X-A-B;

D-A-B-Y-Z;

A-B-Y-Z;

D-A-B-E;

D-A-B; and

A-B-D;

wherein:

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid

residue;

A is Lys, Arg or His;

B is Glu or Asp;

C is a carrier compound residue;

5 Z is a carrier compound residue.

56. A method as recited in claim 55, wherein said patient is suffering from one or more condition selected from the group consisting of:

(a) septic shock;

(b) multiple sclerosis;

10 (c) lupus erythematoses;

(d) auto-immune disease;

(e) replacement of corticosteroid and hydrocortisteroid in the therapy of auto-immune and dermatological indications where these steroids were used to induce immuno-suppression; and

15 (f) graft vs, host disease to reduce immune activity in organ and tissue transplant rejection.

57. A method of reducing immune response in a patient in need of such treatment, comprising administering to said patient an immune response reducing effective amount of a pharmaceutical formulation

20 comprising at least one compound selected from the group consisting of:

C-X-H-A-B-Y-Z;

C-X-H-A-B-D;

C-X-H-A-B;

D-H-A-B-Y-Z;

25 H-A-B-Y-Z;

D-H-A-B-E;

D-H-A-B;

A-B-H-D;

C-X-A-B-H-Y-Z;

30 C-X-A-B-H-D;

C-X-A-B-H;

D-A-B-H-Y-Z;

A-B-H-Y-Z;

D-A-B-H-E;

5 D-A-B-H; and

A-B-H-D;

wherein:

H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

10 X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

15 D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

20 C is a carrier compound residue;

Z is a carrier compound residue.

58. A method of vaccinating against at least one immunosuppressive amino acid sequence selected from the group consisting of:

25 Asp-Arg-Ala-Ala-Asp-Gly-Gln-Pro-Ala-Gly; (SEQ ID NO. 1)

HTLV-I gp21E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Trp-Glu-Gln-Gly-Gly-Leu-Cys-Lys-Ala-Leu-Gln-Glu-Gly-Cys-Arg-Phe; (SEQ ID NO. 2)

30 HTLV-II gp21E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Trp-Glu-Gln-Gly-Gly-Leu-Cys-Lys-Ala-Ile-Gln-Glu-Glu-Cys-Cys-Phe; (SEQ ID NO. 3)

MoLV p15E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Leu-
Lys-Glu-Gly-Gly-Leu-Cys-Ala-Ala-Leu-Lys-Glu-Glu-Cys-Cys-Phe; (SEQ ID
NO. 4)

FeLV p15E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Ile-Leu-Phe-Leu-
5 Gln-Glu-Gly-Gly-Leu-Cys-Ala-Ala-Leu-Lys-Glu-Glu-Cys-Cys-Phe; (SEQ ID
NO. 5) and

Vivax-1

the immunosuppressive effect of which is caused by the presence in said at
least one sequence of one or more positive/negative group, defined as a
10 two-amino acid sub-sequence where a positive amino acid selected from
Lys, Arg and His is adjacent to a negative amino acid selected from Glu
and Asp, in a patient in need of such vaccination, comprising administering
to said patient an immunosuppressive sequence vaccinating effective
amount of a pharmaceutical formulation comprising at least one modified
15 sequence, said modified sequence comprising a compound which is
identical to said at least one immunosuppressive sequence, except that at
least one amino acid residue of the two amino acid residues in said one or
more positive/negative group is replaced with:

an antimetabolite of said at least one amino acid residue;
20 the D-isomer of said at least one amino acid residue; or
an analog of said at least one amino acid residue.

59. A method of vaccinating against at least one
immunosuppressive amino acid sequence which, when present in an
animal, adversely affects the immune response of said animal, said
25 sequence having a formula selected from the group consisting of:

$R-[M-R]_n$;
 $[M-S]_n$; and
 $[R-M]_n$;

wherein:

30 n is a positive integer;
each R is, independently an amino acid sub-sequence comprising at

- least one amino acid residue;
- each M is independently selected from Lys-Glu, Lys-Asp, Arg-Glu, Arg-Asp, His-Glu, His-Asp, Glu-Lys, Asp-Lys, Glu-Arg, Asp-Arg, Glu-His and Asp-His;
- 5 wherein the immunosuppressive effect of said at least one immunosuppressive amino acid sequence is caused by the presence in the sequence of the one or more instance of an M group, in a patient in need of such vaccination, comprising administering to said patient an immunosuppressive sequence vaccinating effective amount of a
- 10 pharmaceutical formulation comprising at least one compound which is identical to said at least one immunosuppressive sequence, except that at least one amino acid residue of the two amino acid residues in said one or more instance of an M group is replaced with an antimetabolite of said at least one amino acid residue, the D-isomer of said at least one amino acid
- 15 residue, or an analog of said at least one amino acid residue.

60. A method of treating a condition selected from the group consisting of:

- (a) immunodeficiency resultant from a viral infection;
- (b) immunodeficiency resultant from one or more of the following.

20 bacterial, mycoplasmic, fungal and/or parasitic infections;
- (c) immunodeficiency resultant from the growth of neoplastic tissue;
- (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
- 25 (e) myalgic encephalomyelitis (ME);
- (f) post inoculation or viral infection fatigue syndrome;
- (g) tuberculosis infection; and
- (h) malarial infection,

in a patient in need of such treatment, comprising deleting genetic

30 material from an infectious organism to prevent said genetic material from generating one or both amino acids in an amino acid sub-sequence

selected from the group consisting of Lys-Glu, Lys-Asp, Arg-Glu, Arg-Asp, His-Glu, His-Asp, Glu-Lys, Asp-Lys, Glu-Arg, Asp-Arg, Glu-His and Asp-His.

61. A method of treating a condition selected from the group consisting of:
- (a) immunodeficiency resultant from a viral infection;
 - (b) immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections;
 - (c) immunodeficiency resultant from the growth of neoplastic tissue;
 - (d) immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient;
 - (e) myalgic encephalomyelitis (ME);
 - (f) post inoculation or viral infection fatigue syndrome;
 - (g) tuberculosis infection; and
 - (h) malarial infection,
- in a patient in need of such treatment, comprising deleting genetic material from an infectious organism to prevent said genetic material from generating one or more amino acids in an amino acid sub-sequence selected from the group consisting of:
- H-K;
 - K-H; and
 - H-K-H;
- wherein each H is independently selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;
- K is selected from the group consisting of Lys-Glu, Lys-Asp, Arg-Glu, Arg-Asp, His-Glu, His-Asp, Glu-Lys, Asp-Lys, Glu-Arg, Asp-Arg, Glu-His and Asp-His.

62. Polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group

consisting of:

C-X-A-B-Y-Z;

C-X-A-B-D;

C-X-A-B;

5 D-A-B-Y-Z; and

A-B-Y-Z;

wherein:

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

10 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

15 B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

63. Polyclonal or monoclonal antibody as recited in claim 62, wherein said at least one compound consists of 16 or fewer amino acid
20 residues.

64. Polyclonal or monoclonal antibody as recited in claim 62, wherein said at least one compound consists of 8 or fewer amino acid residues.

65. Polyclonal or monoclonal antibody as recited in claim 62,
25 wherein said at least one compound consists of 4 or fewer amino acid residues.

66. Polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group

consisting of:

D-A-B-E;

D-A-B; and

A-B-E;

5

wherein:

D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid residue;

10

A is Lys, Arg or His;

B is Glu or Asp;

and wherein said at least one compound comprises at least 4 amino acid residues.

67. Polyclonal or monoclonal antibody as recited in claim 66,
15 wherein said at least one compound consists of 16 or fewer amino acid residues.

68. Polyclonal or monoclonal antibody as recited in claim 66,
wherein said at least one compound consists of 8 or fewer amino acid residues.

20 69. A peptide having the formula R1-R2-R3-R4, wherein
R1 is a region of up to 5AA within which there is one to three AA
from the group Lysine and/or Arginine;
R2 is a short region of up to 2AA which does not contain any of the
following: Asp, Glu, Lys, Arg or His;
25 R3 is a region of up to 7AA within which there may be one or two AA
from the group Aspartic acid and/or Glutamic acid, wherein the Aspartic
acid or Glutamic closest to the R4 region is positioned within R3 to allow a
minimum of two AA between these said acids and the R4 region; and
R4 is a region of two AA containing one AA of either Lysine or

Arginine attaching to region R3 and the other AA is either Aspartic acid or Glutamic acid.

70. A pharmaceutical composition comprising at least one compound selected from the group consisting of:

5 C-X-A-B-Y-Z;

C-X-A-B-D;

C-X-A-B;

D-A-B-Y-Z;

A-B-Y-Z;

10 D-A-B-E;

D-A-B; and

A-B-D;

wherein:

15 X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

20 E is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

B is Glu or Asp;

C is a carrier compound residue;

25 Z is a carrier compound residue.

71. A compound selected from the group consisting of:
compounds corresponding to:

Asp-Arg-Ala-Ala-Asp-Gly-Gln-Pro-Ala-Gly; (SEQ ID NO. 1)

HTLV-I gp21E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Trp-
30 Glu-Gln-Gly-Gly-Leu-Cys-Lys-Ala-Leu-Gln-Glu-Gly-Cys-Arg-Phe; (SEQ ID

NO. 2)

HTLV-II gp21E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Trp-
Glu-Gln-Gly-Gly-Leu-Cys-Lys-Ala-Ile-Gln-Glu-Gln-Cys-Cys-Phe; (SEQ ID
NO. 3)

5 MoLV p15E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Leu-Leu-Phe-Leu-
Lys-Glu-Gly-Gly-Leu-Cys-Ala-Ala-Leu-Lys-Glu-Glu-Cys-Cys-Phe; (SEQ ID
NO. 4)

FeLV p15E Gln-Asn-Arg-Arg-Gly-Leu-Glu-Ile-Leu-Phe-Leu-
Gln-Glu-Gly-Gly-Leu-Cys-Ala-Ala-Leu-Lys-Glu-Glu-Cys-Cys-Phe; (SEQ ID
10 NO. 5) and

Vivax-1

wherein at least one sub-sequence of two amino acid residues where a
positive amino acid selected from Lys, Arg and His is adjacent to a
negative amino acid selected from Glu and Asp, is replaced with at least
15 one modified sequence, said modified sequence comprising a compound
which is identical to said at least one sub-sequence, except that at least
one amino acid residue of the two amino acid residues in said one or more
positive/negative group is replaced with:

an antimetabolite of said at least one amino acid residue;
20 the D-isomer of said at least one amino acid residue; or
an analog of said at least one amino acid residue.

72. A peptide having the formula RA-RB-RC-RD, wherein:

RA is a region of up to 5 AA within which there is one to three AA
from the group Lysine and/or Arginine;

25 RB is a short region of up to 2AA which does not contain any of Asp,
Glu, Lys, Arg or His;

RC is a region of up to 7AA within which there may be one or two AA
from the group Aspartic acid and/or Glutamic acid wherein the Asp or Glu
closest to the RD region is positioned within RC to allow a minimum of two
30 AA between this said AA, if one exists, and the RD region; and

RD is a region of three or four AA containing one AA of either Lysine

or Arginine attaching to region RC and one or two amino acids in the middle of the region containing AA from Polar and/or non-Polar with another AA at the end of the region which is either Asp or Glu.

73. A pharmaceutical composition comprising at least two Th₂
5 cytokines.

74. A pharmaceutical composition as recited in claim 73, wherein said at least two Th₂ cytokines include Interleukin 10 and Interleukin 4.

75. A pharmaceutical composition comprising Interleukin 10,
Interleukin 4 and at least one of antagonist of Interleukin 10 and antagonist
10 of Interleukin 4.

76. A pharmaceutical composition comprising Interleukin 10,
Interleukin 4 and at least one of agonist of Interleukin 10 and agonist of
Interleukin 4.

77. A pharmaceutical composition comprising anti-serum to
15 Interleukin 10 and anti-serum to Interleukin 4.

78. A pharmaceutical composition comprising anti-serum to
Interleukin 10 and at least one of antagonist of Interleukin 4 and agonist of
Interleukin 4.

79. A pharmaceutical composition comprising anti-serum to
20 Interleukin 4 and at least one of antagonist of Interleukin 10 and agonist of
Interleukin 10.

80. Polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

C-X-A-Q-B-Y-Z;
C-X-A-Q-B-D;
C-X-A-Q-B;
D-A-Q-B-Y-Z; and
5 A-Q-B-Y-Z;

wherein:

Q is a sub-sequence consisting of one or two amino acid residues;

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

10 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

15 B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

81. Polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group
20 consisting of:

D-A-Q-B-E;

D-A-Q-B; and

A-Q-B-E;

wherein:

25 Q is a sub-sequence consisting of one or two amino acid residues;

D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid residue;

30 A is Lys, Arg or His;

B is Glu or Asp;

and wherein said at least one compound comprises at least 4 amino acid residues.

82. Polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group

5 consisting of:

C-X-A-Q-B-Y-Z;

C-X-A-Q-B-D;

C-X-A-Q-B;

D-A-Q-B-Y-Z; and

10 A-Q-B-Y-Z;

wherein:

Q is a sub-sequence consisting of one or two amino acid residues;

X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

15 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;

20 B is Glu or Asp;

C is a carrier compound residue;

Z is a carrier compound residue.

83. Polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group

25 consisting of:

D-A-Q-B-E;

D-A-Q-B; and

A-Q-B-E;

wherein:

30 Q is a sub-sequence consisting of one or two amino acid residues;

D is an amino acid sub-sequence comprising at least one amino acid residue;

E is an amino acid sub-sequence comprising at least one amino acid residue;

5 A is Lys, Arg or His;

 B is Glu or Asp;

 and wherein said at least one compound comprises at least 4 amino acid residues.

84. Polyclonal or monoclonal antibody, or at least one Fab fragment
10 thereof, generated to at least one compound selected from the group consisting of:

 C-X-H-A-Q-B-Y-Z;

 C-X-H-A-Q-B-D;

 C-X-H-A-Q-B;

15 D-H-A-Q-B-Y-Z;

 H-A-Q-B-Y-Z;

 C-X-A-Q-B-H-Y-Z;

 C-X-A-Q-B-H-D;

 C-X-A-Q-B-H;

20 D-A-Q-B-H-Y-Z; and

 A-Q-B-H-Y-Z;

 wherein:

 Q is a sub-sequence consisting of one or two amino acid residues;

 H is selected from the group consisting of Ala, Ile, Leu, Met, Phe,

25 Trp, Val and Tyr;

 X is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

 Y is a covalent bond or an amino acid sub-sequence comprising at least one amino acid residue;

30 D is an amino acid sub-sequence comprising at least one amino acid residue;

A is Lys, Arg or His;
B is Glu or Asp;
C is a carrier compound residue;
Z is a carrier compound residue.

- 5 85. Polyclonal or monoclonal antibody, or at least one Fab fragment thereof, generated to at least one compound selected from the group consisting of:

 D-H-A-Q-B-E;
 D-H-A-Q-B;
10 H-A-Q-B-E;
 D-A-Q-B-H-E;
 D-A-Q-B-H; and
 A-Q-B-H-E;

 wherein:

- 15 Q is a sub-sequence consisting of one or two amino acid residues;
 H is selected from the group consisting of Ala, Ile, Leu, Met, Phe, Trp, Val and Tyr;

 D is an amino acid sub-sequence comprising at least one amino acid residue;

- 20 E is an amino acid sub-sequence comprising at least one amino acid residue;

 A is Lys, Arg or His;

 B is Glu or Asp;

- 25 and wherein said at least one compound comprises at least 4 amino acid residues.

86. A method of assaying body fluid from an animal, comprising contacting said body fluid with at least one antibody as recited in claim 62 or claim 66.

87. A method of screening a vaccine, comprising contacting said

vaccine with at least one antibody as recited in claim 62 or 66.

88. A method of treatment of a patient, either animal or human against any one or more of the following indications or infections listed below.

- 5 (a) Immunodeficiency resultant from a viral infection.
- (b) Immunodeficiency resultant from one or more of the following, bacterial, mycoplasmic, fungal and/or parasitic infections.
- (c) Immunodeficiency resultant from the growth of neoplastic tissue.
- 10 (d) Immunodeficiency resultant from any cytokine or hormone imbalance or imbalance of any natural product within the patient.
- (e) Myalgic Encephalomyelitis (ME).
- (f) Post inoculation or viral infection fatigue syndrome.
- (g) Tuberculosis infection.
- 15 (h) Malarial infection.

wherein the treatment comprises administering an effective dosage of a pharmaceutical formulation comprising polyclonal or monoclonal antibodies generated to any one or more sequences selected from the group consisting of:

- 20 Ala-His-Asp; Ala-His-Glu; Ala-Lys-Asp; Ala-Lys-Glu; Ala-Arg-Asp; Ala-Arg-Glu; Ile-His-Asp; Ile-His-Glu; Ile-Lys-Asp; Ile-Lys-Glu; Ile-Arg-Asp; Ile-Arg-Glu; Leu-His-Asp; Leu-His-Glu; Leu-Lys-Asp; Leu-Lys-Glu; Leu-Arg-Asp; Leu-Arg-Glu; Met-His-Asp; Met-His-Glu; Met-Lys-Asp; Met-Lys-Glu; Met-Arg-Asp; Met-Arg-Glu; Phe-His-Asp; Phe-His-Glu; Phe-Lys-Asp;
- 25 Phe-Lys-Glu; Phe-Arg-Asp; Phe-Arg-Glu; Pro-His-Asp; Pro-His-Glu; Pro-Lys-Asp; Pro-Lys-Glu; Pro-Arg-Asp; Pro-Arg-Glu; Trp-His-Asp; Trp-His-Glu; Trp-Lys-Asp; Trp-Lys-Glu; Trp-Arg-Asp; Trp-Arg-Glu; Val-His-Asp; Val-His-Glu; Val-Lys-Asp; Val-Lys-Glu; Val-Arg-Asp; Val-Arg-Glu; Ala-Asp-His; Ala-Glu-His; Ala-Asp-Lys; Ala-Glu-Lys;
- 30 Ala-Asp-Arg; Ala-Glu-Arg; Ile-Asp-His; Ile-Glu-His; Ile-Asp-Lys; Ile-Glu-Lys; Ile-Asp-Arg; Ile-Glu-Arg; Leu-Asp-His; Leu-Glu-His; Leu-Asp-Lys;

Leu-Glu-Lys; Leu-Asp-Arg; Leu-Glu-Arg; Met-Asp-His; Met-Glu-His;
Met-Asp-Lys; Met-Glu-Lys; Met-Asp-Arg; Met-Glu-Arg; Phe-Asp-His;
Phe-Glu-His; Phe-Asp-Lys; Phe-Glu-Lys; Phe-Asp-Arg; Phe-Glu-Arg;
Pro-Asp-His; Pro-Glu-His; Pro-Asp-Lys; Pro-Glu-Lys; Pro-Asp-Arg;
5 Pro-Glu-Arg; Trp-Asp-His; Trp-Glu-His; Trp-Asp-Lys; Trp-Glu-Lys;
Trp-Asp-Arg; Trp-Glu-Arg; Val-Asp-His; Val-Glu-His; Val-Asp-Lys;
Val-Glu-Lys; Val-Asp-Arg; and Val-Glu-Arg.

89. A method of treatment of a patient, either animal or human
against any one or more of the following indications:

- 10 (a) Septic Shock
- (b) Multiple Sclerosis
- (c) Lupus Erythematoses
- (d) Auto-immune diseases - myasthema gravis, rheumatoid
arthritis, sjogrens disease
- 15 (e) Replacement of corticosteroid and hydrocortisteroid in the
therapy of auto-immune and dermatological indications where these
steroids were used to induce immuno-suppression.
- (f) Graft v host disease to reduce immune activity in organ and
tissue transplant rejection.
- 20 The treatment comprises administration of an effective dosage of
pharmaceutical formulation wherein the active constituent is one or more of
the amino-acid charged ion bridge pairs attached to a hydrophobic amino
acid or acids as outlined herein table

90. A method of preparation of a prophylactic vaccine antigen
25 using inactivated coat or capsid peptides. Since vaccine preparations
whose antigens contain the specified ion bridge pair hydrophobic amino
acid sequences identified in the patient will not be capable of engendering
protective immunity this preparation method for a vaccine that will produce
both T & B cell memory response requires that when preparing the
30 antigenic peptide it is necessary to delete or otherwise neutralise these

specific sequences by the use of antibodies or deletion during synthesis. In live vaccine organism generation or synthesis this may be achieved by using anti-sense RNA and/or DNA strands to prevent synthesis in the organism of these cytokine like messenger signal sequences thus

5 producing a viable infecting organism for use in vaccine preparation but one without the means to effect immunosuppression or avoidance of the T cell defendant immune system deletion chiron corporation malaria vaccine. Antigen Vivax-1 and SmithKline Beecham Malaria Vaccine NSI₈₁ V20 sequence Asp-Arg-Ala-Ala-Asp-Gly-Gln-Pro-Ala-Gly (SEQ ID

10 NO. 6)

both contain the specified sequences which are immunologically privileged and act as cytokine signal molecules similar to AFP and Interleukin 10. If these sequences are deleted and the vaccine antigen for malaria contained only the plasmodium vivax circumsporozoite (CS) protein minus ion bridge

15 pairs associated with hydrophobic amino acid/or acids together with antibodies to these specific sequences as outlined in earlier claims then a proper response by both the T & B cell components of the immune system can be expected which will confer immunity. Another method capable of conferring immunity to infection by organisms which have previously

20 resisted efforts to be good vaccine candidates and this applies to organisms such as Plasmodium which causes human malaria and to the HIV-1 HHV and influenza virus is to culture these organisms in the presence of antisense RNA or DNA to these specific sequences and then use the inactivated organisms produced to act as vaccine antigen. Also it

25 is possible to make deletions to the infectious organisms genetic material so preventing it from generating these specific sequences, such genetically modified organisms could be used because they would infect, replicate and generate an immune system attack which would completely remove the infection since it would have been disarmed by not having these

30 sequences to allow it shift the balance of the hosts immune attack on it and the vaccinated subject would retain a balanced complement of B & T cell memory defences against further infection.

91. A method whereby polyclonal or monoclonal antibodies generated to the specific sequences listed under Claim X can be used as a blood/serum or body fluid assay to determine the levels of these specific peptides since no antibody response would be expected by the affected human since these specific sequences are immunologically privileged and do not present as foreign. Since we have identified elevated levels of these peptides in patients suffering from Myalgic Encephalomyelitis this assay could be used for both diagnosis and for determining the progress of therapy in these and other conditions where elevated levels of these peptide cause disease states.

92. A method of immune treatment in human and/or animal with pharmaceutical formulations containing in whole or in part polyclonal or monoclonal antibodies generated to amino acid sequences which exhibit specific ion bridge charged pair arrays of a positively charged amino acid and a negatively charged amino acid aligned together enclosed on one or both sides by a hydrophobic transmembrane segment of amino acids. There may be more than one ion bridge pair separated by polar or non-polar amino acids present within the peptide to which the antibodies are generated.

93. A method of immune treatment in human and/or animal with a pharmaceutical formulation containing in whole or in part polyclonal or monoclonal antibodies generated to the peptide of sequence
Leu-Arg-Asp-Leu-Arg-Asp-Ala (SEQ ID NO. 7)
which encloses two ion bridge pairs within non-polar amino acids on both sides.

94. A method of immune treatment in human and/or animal with a pharmaceutical formulation containing in whole or in part polyclonal or monoclonal antibodies generated to the specific peptide sequence
Val-Glu-Arg-Tyr-Leu-Lys-Asp-Gln (SEQ ID NO. 8)

which encloses two ion bridge pairs within both polar and non-polar amino acids.

95. A method of immune treatment in human and/or animal with a pharmaceutical formulation containing in whole or in part polyclonal or
5 monoclonal antibodies generated to one or a combination of these specific peptide sequences:

- (a) Pro-Lys-Glu-Ile-Ala (SEQ ID NO. 9)
- (b) Ala-Asp-Lys-Val-Met (SEQ ID NO. 10)
 - Val-Glu-Lys-Tyr (SEQ ID NO. 11)
 - 10 Leu-Glu-Lys-Tyr (SEQ ID NO. 12)
 - Tyr-Asp-Lys-Ile (SEQ ID NO. 13)
 - Leu-Glu-Lys-Ile (SEQ ID NO. 14)
 - Ser-Glu-Arg-Leu (SEQ ID NO. 15)
 - Gly-Glu-Lys-Ile (SEQ ID NO. 16)
 - 15 Leu-Glu-Arg-Gly (SEQ ID NO. 17)
 - Tyr-Glu-His-Val (SEQ ID NO. 18)
 - Leu-Glu-Lys-Cys (SEQ ID NO. 19)
 - Gly-Asp-Arg-Ala (SEQ ID NO. 20)
 - Gly-Glu-Lys-Leu (SEQ ID NO. 21)
 - 20 Thr-Glu-Arg-Val (SEQ ID NO. 22)
 - Thr-Asp-Arg-Val (SEQ ID NO. 23)
 - Val-Glu-Arg-Tyr (SEQ ID NO. 24)
 - Gln-Asp-Lys-Leu (SEQ ID NO. 25)
 - Thr-Glu-His-Leu (SEQ ID NO. 26)
 - 25 Leu-Asp-Arg-Leu (SEQ ID NO. 27)
 - Phe-Glu-Lys-Thr (SEQ ID NO. 28)
 - Ser-Arg-Asp-Leu (SEQ ID NO. 29)
 - Leu-Glu-Lys-Tyr (SEQ ID NO. 30)
 - Asn-Glu-Arg-Leu (SEQ ID NO. 31)
 - 30 Ile-Glu-Lys-Thr (SEQ ID NO. 32) and
 - Asn-Glu-Lys-Phe (SEQ ID NO. 33).

96. A method according to Claims 88-91 wherein said antigenic peptide is selected from the group consisting in whole or in part, of human, animal, synthetic or recombinant alpha-fetoprotein (AFP) and/or cytokine inhibitory factor (Interleukin 10), Malaria circumsporozite, Viral peptides.

5 97. A method for treating a patient, comprising administering a pharmaceutical formulation containing polyclonal and/or monoclonal antibodies to sequences as specified in Claims 88-91 as a therapeutic for the binding and removal of peptides generated by the infected host or
10 infecting organism which have been specifically enhanced by the infecting organism to render a down regulation in Th₁ cell type dependent immune resistance to infection.

98. A method as recited in any one of claims 1-61 and 88-97, further comprising administering to said patient an antiviral therapy.

99. A method as recited in claim 98, wherein said antiviral therapy
15 comprises administration of AZT.

100. A pharmaceutical composition as recited in any one of claims 70 and 73-79, further comprising administering to said patient an antiviral material.

101. A pharmaceutical formulation as recited in claim 100, wherein
20 said antiviral material comprises AZT.

102. A pharmaceutical formulation comprising at least one antibody as recited in any one of claims 62-68 and 80-85, together with an antiviral material.

103. A pharmaceutical formulation as recited in claim 102, wherein
25 said antiviral material comprises AZT.

104. A pharmaceutical formulation comprising at least one peptide as recited in any one of claims 69 and 72, together with an antiviral material.

105. A pharmaceutical formulation as recited in claim 104, wherein
5 said antiviral material comprises AZT.

106. A pharmaceutical formulation comprising at least one compound as recited in claim 71, together with an antiviral material.

107. A pharmaceutical formulation as recited in claim 106, wherein said antiviral material comprises AZT.

108. A treatment for animals and humans suffering from
10 immunosuppressive disease whereby the patient is administered a cellular receptor to a Th₂ cytokine.

109. A treatment for animals and humans suffering from
15 immunosuppressive disease whereby the patient is administered cellular receptors to two or more Th₂ cytokine in a combination therapy.

110. A treatment according to claim 108 or 109 wherein the immunosuppressive disease is resultant from a viral infection.

111. A treatment according to Claim 108 or 109 wherein the immunosuppressive disease is resultant from a bacterial infection.

112. A treatment according to Claim 108 or 109 wherein the
20 immunosuppressive disease is resultant from a fungal infection.

113. A treatment according to Claim 108 or 109 where the cellular receptor to the Th₂ cytokine is one or more of the following Interleukin-4

receptor, Interleukin-6 receptor and/or Interleukin-10 receptor.

114. A treatment according to Claim 109 wherein the cellular receptors to the cytokines are administered in a specific ratio dependant on the disease state.

5 115. A treatment according to any one of Claims 108-113 wherein the cellular receptor to the cytokines is administered by IV, enema or transdermal patch in dose amounts of between 10-500 ug per day.

116. A treatment according to any one of claims 108-113 wherein the cellular receptor to the cytokines is administered as a soluble receptor.

10 117. A treatment according to claim 108 or 109 wherein the treatment is for the removal of Th₂ cytokines/AFP immunosuppressive mimic peptides of viral/vacterial or parasitic origin.

118. A method of achieving improved immune response in a patient, said method comprising administering an amount of an antagonist,
15 in the form of an amino acid sequence of greater than two amino acids in length, of Interleukin 10 (IL-10) or part thereof wherein one or more of the negatively charged R groups of IL-10 is a D amino acid.

119. A method of achieving improved immune response in a patient, said method comprising administering an amount of an antagonist,
20 in the form of an amino acid sequence of greater than two amino acids in length, of Interleukin 10 (IL-10) or part thereof wherein one or more of the positively charged R groups of IL-10 is a D amino acid.

120. A method of achieving improved immune response in a patient, said method comprising administering an amount of an antagonist,
25 in the form of an amino acid sequence of greater than two amino acids in

length, of Interleukin 10 (IL-10) or part thereof wherein one or more of each of the negatively and positively charged R groups of IL-10 is a D amino acid.

121. A method of achieving improved immune response in a
5 patient, said method comprising administering an amount of an antagonist, in the form of an amino acid sequence of greater than two amino acids in length, of Interleukin 10 (IL-10) or part thereof wherein one or more of the polar uncharged R groups of IL-10 is a D amino acid.

122. A method of achieving improved immune response in a
10 patient, said method comprising administering an amount of an antagonist, in the form of an amino acid sequence of greater than two amino acids in length, of Interleukin 10 (IL-10) or part thereof wherein one or more of the non-polar uncharged R groups of IL-10 is a D amino acid.

123. A method of achieving improved immune response in a
15 patient, said method comprising administering an amount of an antagonist, in the form of an amino acid sequence of greater than two amino acids in length, of Interleukin 10 (IL-10) or part thereof wherein one or more of each of the non-polar and polar uncharged R groups of IL-10 is a D amino acid.

124. A method of achieving improved immune response in a
20 patient, said method comprising administering an amount of an antagonist, in the form of an amino acid sequence of greater than two amino acids in length, of Interleukin 10 (IL-10) or part thereof wherein one or more of each of the negatively charged, non-polar and polar uncharged R groups of IL-10 is a D amino acid.

25 125. A method of achieving improved immune response in a patient, said method comprising administering an amount of an antagonist, in the form of an amino acid sequence of greater than two amino acids in

length, of Interleukin 10 (IL-10) or part thereof wherein one or more of each of the positively charged, non-polar and polar uncharged R groups of IL-10 is a D amino acid.

126. A method of achieving improved immune response in a
- 5 patient, said method comprising administering an amount of an antagonist, in the form of an amino acid sequence of greater than two amino acids in length, of Interleukin 10 (IL-10) or part thereof wherein one or more of each of the positively charged, negatively charged, non-polar and polar uncharged R groups of IL-10 is a D amino acid.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 4/00, 5/08, 7/08, 14/54, 16/24, A61K 38/20, 39/385, 39/395	A3	(11) International Publication Number: WO 98/10787 (43) International Publication Date: 19 March 1998 (19.03.98)
(21) International Application Number: PCT/IB97/01086 (22) International Filing Date: 10 September 1997 (10.09.97) (30) Priority Data: 60/025,180 11 September 1996 (11.09.96) US (71)(72) Applicant and Inventor: PRENDERGAST, Patrick, T. [IE/IE]; Baybush, Straffan, County Kildare (IE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 30 July 1998 (30.07.98)
(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF IMMUNE DISORDERS		
(57) Abstract <p>Herein is described a specific amino acid sequence which exhibits specific Ion (bridge) pair arrays enclosed on at least one side by non polar hydrophobic transmembrane segments, as a mechanism used by many infectious agents and a number of cytokine inhibitory factors, such as Interleukin 10 and Prolactin Inhibitory factor and alfa-fetoprotein, to not only undermine the hosts immune defences but to also allow for the infection of target lymphoid tissue. It has been demonstrated that certain vaccines, when inoculated into a host, produced a range of neutralising antibodies but failed to prevent infection when that host is later challenged with live infectious organism. This present patent illustrates that when such vaccine inoculation is coupled with passive immunisation with mono or polyclonal antibodies to these specific amino acid sequences as specified herein that the host is then capable of overcoming the infectious challenge. Herein is described the therapeutic use of mono or polyclonal antibodies to these said specific sequences as a treatment for Acquired Immune Deficiency Syndrome (AIDS) and other disease states that persist due to the presence of a cytokine inhibitory factor of viral, fungal, bacterial or host origin such as Chronic Fatigue Syndrome where Interleukin 10 mimic molecules are responsible for a multitude of disease symptoms identified as indicative of Myalgic Encephalitis. Herein is described the therapeutic use of mono or polyclonal antibodies to these specific amino acid sequences as a combination therapy with vaccines and anti-viral agents to prevent side effects from certain immune modulation and anti-viral agents (e.g. DHEA and IL-12) which cause enhanced production of Interleukin 10 or AFP mimic molecules during therapy. Also herein is described the therapeutic use of these specific sequences either isolated from the organism source or produced by direct synthesis or recombinant protein synthesis. These peptides when administered to a patient suffering from an auto-immune disease, such as Multiple Sclerosis (MS), Lupus (systemic Lupus erythematoses) or diabetes or rheumatoid arthritis as limited examples or to transplant organ recipients, will allow the patient's immune state to be shifted to a Th₂ antibody dependent immune response and curtail the Th₁ (T cell dependent) immune attack which is evident in such immune malfunctions as MS and graft versus host disease. Certain dermatological conditions which are today treated by the use of corticosteroid creams and ointment may also be successfully treated by replacing the corticosteroid with these mimic immunosuppressive AFP/Interleukin 10 sequences outlined in this patent.</p>		

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INTERNATIONAL SEARCH REPORT

Intern. Application No.
PCT/IB 97/01086

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07K4/00 C07K5/08 C07K7/08 C07K14/54 C07K16/24 A61K38/20 A61K39/385 A61K39/395		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 19568 A (M. RATH) 20 July 1995 see page 2, last paragraph - page 3 see page 11 - page 22 see page 24, line 1 ---	1-40, 49-72, 80-97, 102-107
X	EP 0 056 249 A (NEW YORK BLOOD CENTER INC) 21 July 1982 see page 4, line 20 - page 16, line 20 see page 18, line 26 - page 23, line 35 --- -/--	49-54, 58, 80-85, 102,103
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">21 January 1998</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">10.06.98</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">De Kok, A</div>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/01086

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. RATH: "Cationic-anionic and anionic-cationic oligopeptides in apoprotein-A and other proteins as modulators of protein action and of biological communication" JOURNAL OF APPLIED NUTRITION, vol. 44, no. 3-4, 1992, LA HABRA US, pages 62-69, XP002051963 see the whole document	1-40, 49-72, 80-97, 102-107
X	WO 93 11157 A (THE QUEENSLAND INSTITUTE OF MEDICAL RESEARCH) 10 June 1993 see page 9, line 1 - page 20, line 20 see page 30 - page 31	58,71, 98,99, 106,107
X	US 4 822 606 A (R.D. SNYDERMAN ET AL.) 18 April 1989 see column 1, line 10 - column 4, line 14 see column 9 - column 10	58,71, 98,99, 106,107
X	WO 88 05783 A (ORTHO PHARMACEUTICAL CORPORATION) 11 August 1988 see page 5, line 1 - page 7, line 31 see claims 1,3	59,71, 98,99, 106,107
X	WO 95 04075 A (MEDVET SCIENCE PTY LTD ;VADAS MATHEW ALEXANDER (AU); LOPEZ ANGEL F) 9 February 1995 see page 3, line 3 - line 20 see page 6, line 5 - line 18 see page 8; table 2	1,95
X	WO 91 14451 A (SCHERING CORPORATION) 3 October 1991 see page 15	1,23,38, 55,62
X	EP 0 287 226 A (HIVER LTD) 19 October 1988 see page 3, line 46 - page 5, line 22 see page 19, line 40 - page 29, line 55	1,55,62, 80
X	EP 0 323 424 A (J. BLOMBERG ET AL.) 5 July 1989 see abstract	1
P,X	WO 97 26279 A (STEENO RESEARCH GROUP A S) 24 July 1997 see page 1 - page 11	55,56, 70,98,99

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB 97/01086

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-39, 49-61
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-39, 49-61
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: 89, 91
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
Both claims are not clear (Art. 6, PCT)
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-40, 49-72, 80-99, 102-107

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-40, 49-72, 80-99, 102-107

Pharmaceutical compositions containing peptides which exhibit specific ion bridge charged pair arrays of a positively charged amino acid and a negatively charged amino acid or containing polyclonal or monoclonal antibodies or fragments thereof generated to these peptides and their use in the treatment of immune disorders

2. Claims: 41-48, 73-79, 100-101

A pharmaceutical composition comprising at least two Th2 cytokines and its use

3. Claims: 108-117

A pharmaceutical composition comprising a receptor to a Th2 cytokine and its use for the treatment of immunosuppressive disease

4. Claims: 118-126

A pharmaceutical composition comprising an interleukin 10 or part thereof, wherein at least one of the negatively charged R groups is a D amino acid, and its use as antagonist

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. Application No

PCT/IB 97/01086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9519568 A	20-07-95	AU 1681095 A EP 0744027 A	01-08-95 27-11-96
EP 0056249 A	21-07-82	AU 552702 B AU 7941382 A CA 1206094 A JP 57136527 A US 5019383 A US 4554101 A ZA 8200251 A	19-06-86 15-07-82 17-06-86 23-08-82 28-05-91 19-11-85 24-11-82
WO 9311157 A	10-06-93	NONE	
US 4822606 A	18-04-89	NONE	
WO 8805783 A	11-08-88	AU 1366088 A DK 535988 A EP 0300031 A JP 1501939 T	24-08-88 25-11-88 25-01-89 06-07-89
WO 9504075 A	09-02-95	AU 690128 B AU 7341494 A CA 2168261 A EP 0715633 A JP 9501154 T	23-04-98 28-02-95 09-02-95 12-06-96 04-02-97
WO 9114451 A	03-10-91	AT 126704 T AU 650013 B AU 7588291 A CA 2079230 A CN 1056245 A DE 69112392 D DE 69112392 T DK 522010 T EP 0522010 A ES 2076526 T FI 924278 A IE 70910 B JP 2509774 B JP 5501116 T	15-09-95 09-06-94 21-10-91 27-09-91 20-11-91 28-09-95 01-02-96 15-01-96 13-01-93 01-11-95 24-09-92 15-01-97 26-06-96 04-03-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/01086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9114451 A		KR 9604856 B MX 9203522 A OA 9674 A PT 97108 A	16-04-96 01-07-92 15-05-93 29-11-91
EP 0287226 A	19-10-88	AU 620804 B AU 1489188 A AU 1634592 A DK 653388 A FI 885441 A WO 8807375 A JP 1502751 T RU 2014845 C	27-02-92 02-11-88 30-07-92 23-11-88 23-11-88 06-10-88 21-09-89 30-06-94
EP 0323424 A	05-07-89	AU 2913189 A DK 156490 A JP 4503204 T WO 8906240 A	01-08-89 22-08-90 11-06-92 13-07-89
WO 9726279 A	24-07-97	WO 9726278 A AU 1301197 A AU 4385696 A	24-07-97 11-08-97 11-08-97

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